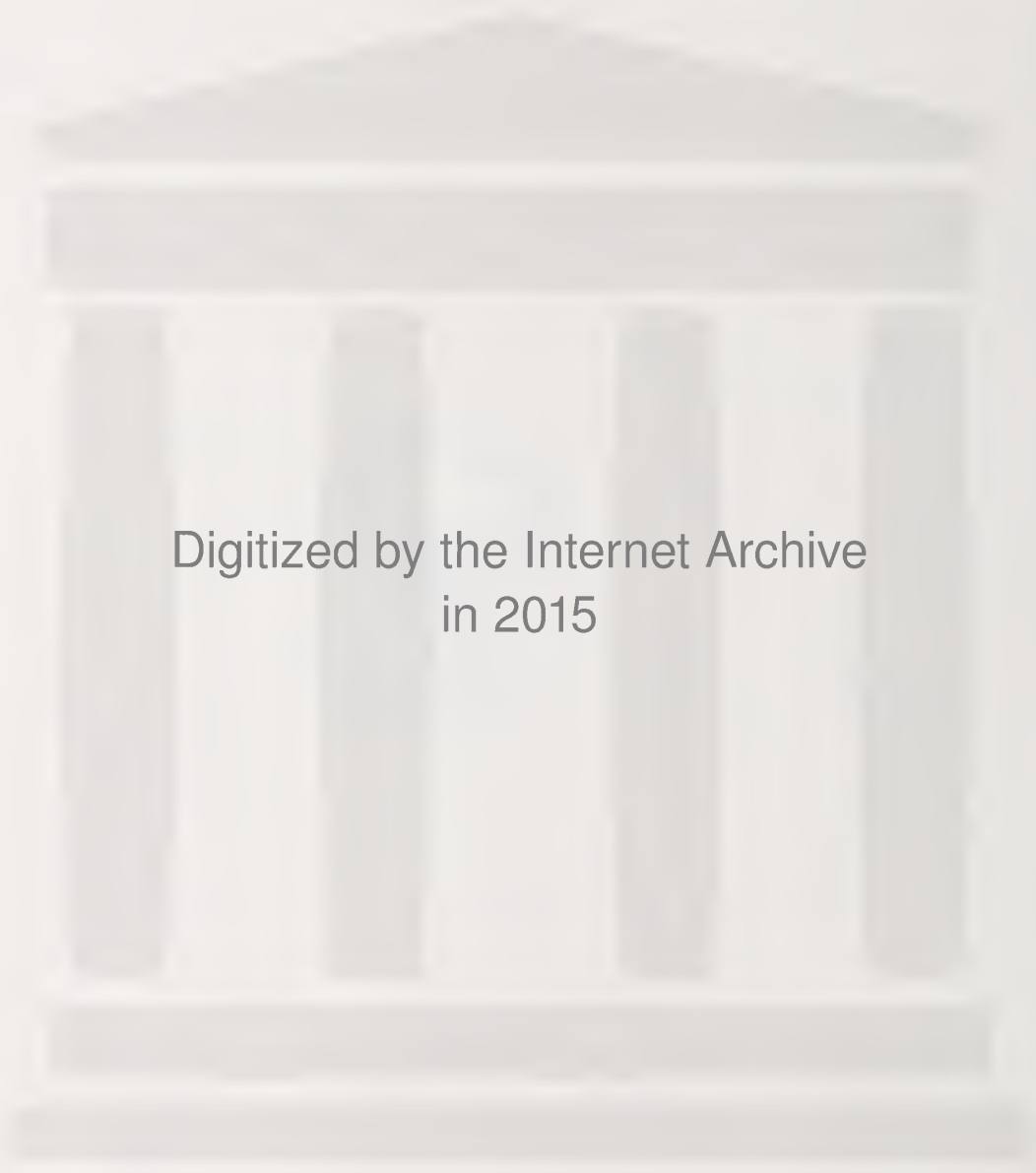




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Endoscopy of the Upper Respiratory And Upper Gastrointestinal Tract

Allan P. Reed, guest editor

From the Department of Anesthesiology of the
Mount Sinai School of Medicine (CUNY)

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Introduction

ALLAN P. REED, M.D.

Associate Professor of Anesthesiology
Mount Sinai School of Medicine

Endoscopy of the Upper Respiratory And Upper Gastrointestinal Tract

FEW INNOVATIONS have had as great an impact on modern medicine as flexible fiberoptic endoscopy. The first fiberoptic endoscope dates back to the 1930s and was employed for gastroscopy. In 1967, Murphy introduced the concept of fiberoptic-assisted endotracheal intubation using a choledochoscope. A year later the father of modern bronchoscopy, Ikeda, working in conjunction with Japan's Machida Endoscope Company and Olympus Optical Company, reported on the use of a new fiberoptic device capable of tip deflection in two directions. Since that time, flexible fiberoptic endoscopes have captured the imagination of anesthesiologists, intensivists, pulmonologists, gastroenterologists, and otolaryngologists, and many refinements have improved the instruments. They now allow clear, well-defined, real-time imagery of the airway and gastrointestinal tract.

Fiberscopes have emerged as irreplaceable diagnostic and therapeutic tools. Astounding visual clarity allows for instantaneous assessment and documentation by still-color and video-color photography. The diagnostic capabilities of the instruments are applicable to a wide range of medical needs, among them diagnosis of tumors; airway obstruction related to stridor, obstructive sleep apnea, hoarseness, and respiratory distress; and endotracheal tube positioning. Therapeutic applications include laser surgery, tracheobronchial drainage, brushings, biopsies, suctioning, endotracheal intubation, and endotracheal tube changes.

It is primarily for intubation that flexible fiberoptic laryngoscopes have captured the interest of anesthesiologists. Flexible fiberoptic laryngoscopes facilitate intubation of the patient who is awake and spontaneously breathing and, in certain circumstances, intubation of the patient who is under general anesthesia as well. The American Society of Anesthesiology recently sponsored a workshop on fiberoptic intubation to foster theoretical and practical expertise related to flexible fiberoptic laryngoscopy. Many of the speakers at this workshop, held June 26–27, 1993, in Boston, have generously adapted their lectures for publication here, where those presentations have been combined with articles on endoscopy in gastroenterology and in otolaryngology in order to bring readers of this journal a review of endoscopy of the upper body.

The articles on the physics of the flexible fiberoptic laryngoscope, preparation for intubation of the awake patient, use of the laryngoscope, critical care applications, predictable problems in use of the laryngoscope, intubation of infants and children, and learning to perform intubation are all composed by anesthesiologists for anesthesiologists. However, the contents of these articles are generally applicable to the work of other specialists who employ flexible fiberoptic technology, and are included for this reason. Additional articles by

other specialists highlight the current use of these devices in various medical fields. This issue includes an article on bronchoscopy of infants and children. A more general anticipated article on bronchoscopy was not submitted, and scheduling

deadlines required publication of this issue without that article. This issue is offered—with that exception—as a state-of-the-art survey of flexible fiberoptic technology in clinical practice.

The Physics of Fiberoptic Endoscopy

STEPHEN F. DIERDORF, M.D.

FIBEROPTIC TECHNOLOGY has diverse applications in medicine and communications. The development of flexible fiberoptic endoscopes has permitted physicians to directly view previously inaccessible areas of the body. These devices have increased the ability to accurately diagnose lesions otherwise identifiable by indirect, often inaccurate techniques. Flexible fiberoptic endoscopes have also provided a method of easily treating some lesions (for example, sclerotherapy for esophageal varices). Fiberoptic technology has been incorporated into the design of rigid bronchoscopes, producing better illumination and magnification of the tracheobronchial tree and proving especially useful for bronchoscopy of infants and children. In addition to imaging devices, fiberoptic systems have been developed that aid in chemical and physical analysis of blood, including pressure and flow measurements (1). Many fiberoptic sensors are used intrinsically (that is, within the body) and therefore differ from traditional extrinsic systems (2). New diagnostic and therapeutic applications for fiberoptic technology in medicine will certainly continue to be introduced.

The discovery that light could travel in a curved line was made in 1854 by John Tyndall, who, in an elaborate experiment, demonstrated that light shining in a tank of water followed a curved stream of water emerging from a hole in the tank (3). He disproved the existing belief that light could travel only in a straight line. However, at that time his discovery had few practical applications. Although patent applications for fiber bundles used for image transmission were filed in 1927, not until the 1950s did Hopkins and

Kapany report the development of a flexible fiberoptic unit that could transmit identifiable images (4, 5). Soon after their report, the first fiberoptic endoscope, a gastroscope, was introduced by Hirschowitz (6). Although it was not initially received with great enthusiasm by the medical profession, the advantages of flexible fiberoptic endoscopy soon became apparent. Prior to the development of fiberoptic scopes, endoscopes were constructed with a series of lenses that offered little magnification and inferior illumination, resulting in an image of poor quality. Consequently, endoscopy was tedious and it was not always possible to adequately examine a suspected lesion. Successful flexible fiberoptic tracheal intubation was first reported in 1967, when a choledochoscope was used for nasotracheal intubation (7). In 1972, a flexible fiberoptic bronchoscope was employed to perform tracheal intubations of awake patients (8). Since that time, the design and construction of fiberoptic endoscopes have been considerably improved. Several manufacturers now produce high-quality flexible fiberoptic instruments that permit the anesthesiologist to successfully intubate patients who have abnormal airway anatomy. Although many alternatives have been developed to facilitate tracheal intubation of the "difficult" airway patient, the flexible fiberoptic laryngoscope is the most reliable and least traumatic. An understanding of the principles of fiberoptic image transmission and the mechanics of fiberscope operation will enhance the beginning endoscopist's mastery of flexible fiberoptic laryngoscopy.

Principles of Fiberoptic Light and Image Transmission

The physical principle that controls light and image transmission through flexible fiberoptic bundles is total internal reflection of light. Light traveling parallel to the fiber axis (meridional

From the Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana. Address reprint requests to the author, Professor of Anesthesiology, Indiana University School of Medicine, 1120 South Drive, Fesler Hall 204, Indianapolis, IN 46202-5115.

rays) passes through the fiber without undergoing reflection. Other light rays that are not parallel to the fiber axis (skew rays) may be internally reflected or refracted (Fig. 1). Normally, as light traverses the boundary between two media such as glass and air, some of the light is internally reflected back into the glass. Some of the light is refracted into the air and is lost to the glass. Light refraction occurs because the speed of light in glass is slower than the speed of light in air. Light traveling from a medium of higher refractive index (glass) to a medium of lower refractive index (air) will be internally reflected at the interface between the media. The amount of light internally reflected in a glass fiber can be increased by coating (cladding) the glass with a substance of lower refractive index. Light rays striking the fiber-cladding interface at an angle greater than the critical angle will be internally reflected (Fig. 2). When virtually all the light is internally reflected through a clad fiber, a waveguide that transmits light is constructed (Fig. 3). Thus, a fiberoptic fiber consists of two parts: the core or light transmission guide and the cladding material (Fig. 4).

Progressive improvements in design and manufacturing techniques have resulted in fibers with only 0.001% light loss per reflection. There is, however, a practical limit to the amount of light that can be transmitted because of light lost at the point of entry (when the light strikes the surface at less than the critical angle), light absorbed by the core glass, and packing fraction loss. The packing fraction is the ratio between the cross-sectional area of the cladding material (cladding does not transmit light) and the cross-sectional area of the core material. Fibers used for laryngoscopes have a core diameter of 6 μm and a cladding thickness of 1.5 μm . Reducing the size of the individual fiber to enhance resolution will increase the packing ratio and decrease light transmission.

Another factor of considerable practical importance in the development of fiberoptic image transmission has been the use of glass with high purity and transparency. For all practical purposes, current manufacturing techniques produce silica-based glass at the theoretical limit of its transparency. A higher degree of transparency will require development of new fiber materials.

Fiberscopes are constructed with bundles of clad fibers. A large number of small fibers are needed to produce a high-quality image. However, fiber density is limited because light loss from the packing fraction (cladding) increases as fiber density increases. In order to transmit only

light, individual fibers in a fiber bundle can be randomly ordered (incoherent). Incoherent fiber bundles are relatively inexpensive to manufacture. Image transmission, however, requires an ordered or coherent fiber arrangement (Fig. 5). A coherent bundle is constructed by precisely arranging the individual fibers so that each fiber is in the same relative location at both ends of the fiber bundle. In contrast to incoherent bundles, coherent bundles are relatively expensive to manufacture.

Components of the Fiberscope

The three basic components of a flexible fiberoptic endoscope are the body, the insertion cord, and the light (transmission) cord (9) (Fig. 6). The body contains the ocular lens (eyepiece), a focusing ring, the working channel sleeve, and the tip deflection lever. The light (transmission) cord transmits light from the light source to the fiberscope. The parts of the insertion cord are of special importance because it is this structure that gives the fiberscope flexibility and permits transmission of a high-quality image. The insertion cord contains the fiberoptic bundles (one or two bundles for light transmission and one bundle for image transmission), the optical system, and the mechanical system (Fig. 7).

Fiber Bundles. There are two types of fiber bundles in the insertion cord: incoherent fibers that function as a light guide to provide illumination at the end of the fiberscope, and coherent fibers that transmit the image.

Both types of fiber bundles are highly flexible, but can be broken if excessive bending occurs. Fiberoptic laryngoscopes typically contain 4,000–6,000 fibers that are each 0.5 mL in diameter. Bronchoscopes, gastroscopes, and colonoscopes are larger in diameter than laryngoscopes and contain more individual fibers and larger fiber bundles.

Optical System. The actual image transmitted by the fiberoptic bundle is quite small (0.3–0.5 mm in diameter) and must be magnified for the endoscopist by a lens system. The lens system is relatively complex and contains an objective lens at the distal end of the fiberscope that magnifies the image. Practical constraints restrict magnification by the objective lens. The image is, however, further enlarged by the ocular lens of the fiberscope's body. The amount of magnification is limited. As magnification increases, individual bundles become visible and distort the image. The eyepiece also contains a diopter adjustment that can be individually altered to compensate for any

Fig. 1. As light meets a glass-air interface, some light is refracted, some is reflected; a, angle of incidence; b, angle of reflection. *Reproduced with permission* from Dierdorf SF. Types and physics of fiberscopes. Anesth Clin North Am 1991; 9(1):19-34.

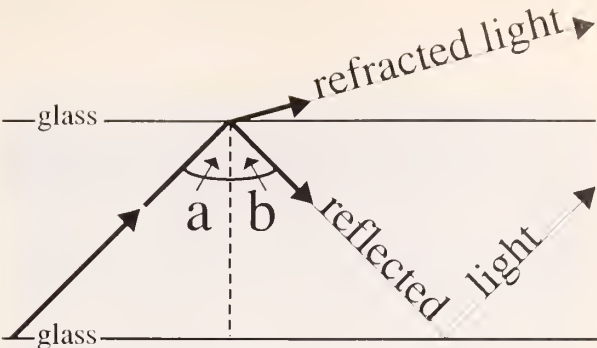


Fig. 2. Light striking boundary of clad glass fiber is internally reflected; I_c , critical angle. Light striking boundary at angle greater than critical angle undergoes total internal reflection. *Reproduced with permission* from Dierdorf SF. Types and physics of fiberscopes. Anesth Clin North Am 1991; 9(1): 19-34.

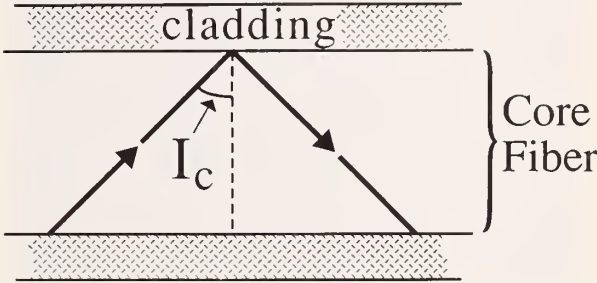


Fig. 3. An unclad fiber loses light throughout its length. Cladding protects interface surface and increases light transmission efficiency. *Reproduced with permission* from Tams T, ed. Small animal endoscopy. St. Louis: C.V. Mosby, 1990:5.

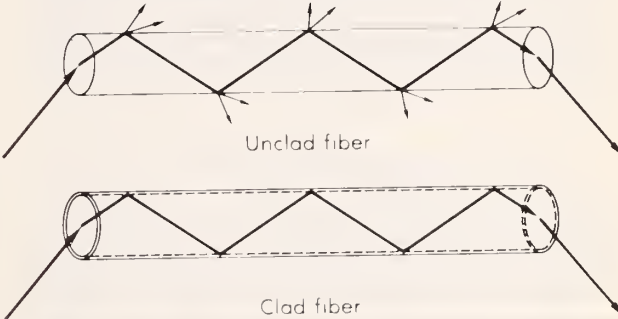
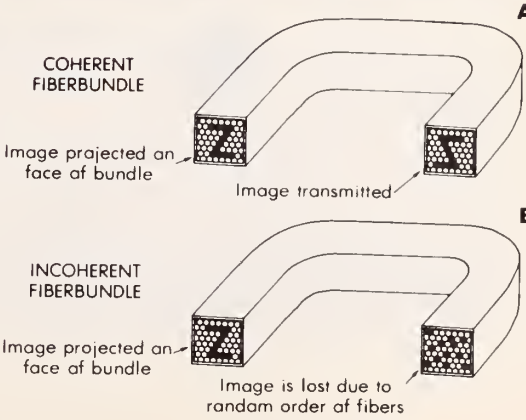


Fig. 4. Extreme magnification of fiberoptic image. Fiber pattern with cladding material is visible. Black dot at nine o'clock position is a broken fiber.



Fig. 5. In coherent fiber bundle, arrangement of fibers in one end of bundle exactly matches arrangement in opposite bundle face (A). In incoherent bundle, no correlation exists between fiber bundles in the two bundle faces (B). *Reproduced with permission* from Tams T, ed. Small animal endoscopy. St. Louis: C.V. Mosby, 1990:7.



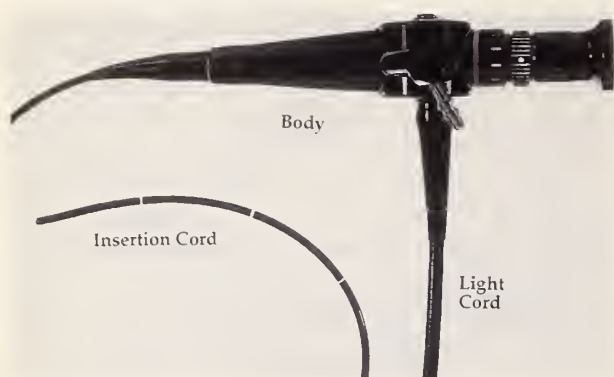


Fig. 6. Three parts of fiberoptic laryngoscope: (1) Body, containing the eyepiece, the working channel sleeve, and the tip deflector (behind); (2) insertion cord, containing the image and light guide bundles; (3) light cord for transmitting light from the light source to the fiberscope. *Reproduced with permission from Anesth Clin North Am 1991; 9(1):23.*

visual abnormality of the endoscopist. The range of focus or depth of field of most fiberoptic laryngoscopes is 3–50 mm. Therefore, the scope can be focused on objects between 3 and 50 mm from its tip.

In addition to size and quality of image, field of view is an important feature. A wide field of view permits better visual field orientation for the endoscopist. Laryngeal position is better correlated with anatomic landmarks through a scope with a wide field of view. However, increasing the field of view reduces the size of the primary image. The proper combination of field of view and image size requires a set of compound lenses in the objective and illumination lenses at the distal end of the scope.

Mechanical System. Although the flexible fiberoptic laryngoscope appears relatively simple in construction, this device is in reality a complex structure containing fiberoptic image and illumination bundles, a working channel, angulation

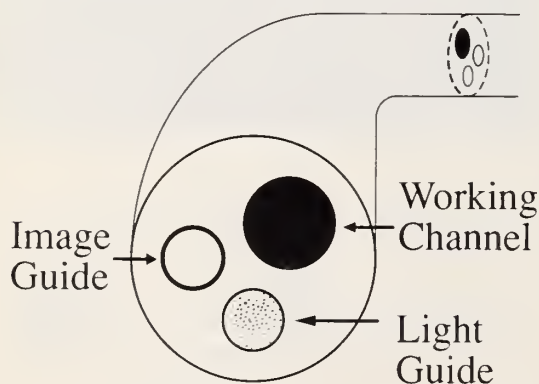


Fig. 7. Diagram of the tip of a fiberoptic laryngoscope demonstrating the relative size and position of insertion cord components. *Reproduced with permission from Anesth Clin North Am 1991; 9(1):28.*

control wires, and a flexible joint system (distal end) ensheathed in a tough, durable outer cover (Fig. 8). The laryngoscope must be rigid enough to pass easily and flexible enough to conform to upper airway anatomy. The distal end of most laryngoscopes and bronchoscopes has an angulation system that permits tip deflection in two directions (up and down). Movement of the tip to the right or left requires rotation of the scope in combination with up or down deflection. Various combinations of tip deflection and scope rotation allow observation of all four visual field quadrants. Gastrosopes and colonoscopes offer larger-diameter insertion tubes, which can accommodate more features. They provide four-way angulation systems permitting movement in four directions with hand controls on the fiberscope's body. The flexible section at the distal end of the scope is constructed of a series of slightly overlapping metal bands attached with an angulation wire. The angulation wire is connected to the deflector lever on the body of the fiberscope. Tip deflection is produced by moving the deflector lever, thus exerting tension on the angulation wire, which, in turn, flexes the metal bands. When the fiberscope is extended, tip deflection occurs in the up and down directions when the control knob is manipulated. However, if the fiberscope is bent upon itself (curled), tip deflection may occur at a 90-degree angle to the vertical plane. This altered directional response is most likely a result of internal twisting of the angulation wire. Considerable variation occurs among different fiberscopes. This variability is a function of the degree of stretching of the angulation control wire that occurs with aging of the fiberscope. Such deviation is significant to the endoscopist because orientation may become lost if tip deflection is unpredictable. The problem of altered tip deflection can be avoided if the fiberscope remains extended during laryngoscopy. In general, improvements in design and manufacture of the angulation system have produced fiberscopes with increased deflection capability.

The working channel runs the length of the endoscope and can be used for a variety of functions. The working channel of most fiberoptic laryngoscopes is 1.2 mm in diameter. Suction can be applied for clearing of secretions, although insufflating oxygen at 3–5 L/min is much more effective for preventing visual field obstruction by secretions. In addition, the low-humidity oxygen keeps the objective lens dry and free of condensate. Local anesthetics can be instilled through the working channel to produce topical anesthetic.

sia of the airway. Working channels of bronchoscopes are 2–4 mm in diameter and accommodate biopsy forceps. These large working channels have also been used for passage of very small bronchoscopes into peripheral airways for diagnosis of distal lung field lesions.

Light Sources

Just as the design of fiberscopes has undergone dramatic improvement in the past 30 years, so has the design of light sources. The original light source for fiberoptic endoscopy was incandescent light. More intense halogen light sources were introduced later. Most recently, xenon light sources have been available (Fig. 9). Xenon light sources are of two types: a manually controlled variable-intensity light, and a manually or automatically controlled light for 35-mm still and video photography. Xenon light sources are often five to ten times more expensive than halogen light sources; in early 1993, a xenon source cost \$4,500. Halogen light sources provide excellent illumination for clinical endoscopy. However, if still or video photography is desired, xenon light sources are essential for adequate illumination. Improvements in light source technology have contributed greatly to the success and wide application of flexible fiberoptic endoscopy.

The light transmission cord that connects the light source to the endoscope can become hot enough to produce third-degree burns if the end of the cord contacts skin. Care must be taken to prevent contact with the patient after the cord is removed from the light source.

Photographic Systems

Still or video photography through endoscopes is performed with increasing frequency for teaching and recording endoscopic findings. Most endoscope manufacturers produce 35-mm cameras or adapters for 35-mm cameras that permit direct attachment to the endoscope. Endoscopists can view the image through a camera viewfinder and expose successive still frames. Video cameras can be attached to the endoscope and the image displayed on a video monitor for teaching applications or storage of diagnostic information (Fig. 10). Many operating rooms already have video equipment for arthroscopic and laparoscopic procedures. Acquisition of the correct adapter permits use of video equipment with most fiberoptic laryngoscopes and bronchoscopes. Sharing of this expensive equipment is cost-effective for all surgical services.



Fig. 8. Fiberoptic colonoscope with plastic sheath removed. **Top** Wire mesh covers distal end. **Bottom** Wire mesh has been removed, demonstrating overlapping metal rings and angulation wires.

Types of Fiberscopes

The desirable size and features of flexible fiberoptic endoscopes depend on the intended application. Since the diameter of the fiberoptic light and image bundles is quite small, the size of the endoscope depends more on the additional components (Fig. 11).

Gastrointestinal Fiberscopes. Gastrosopes and colonoscopes contain 40,000 fibers and range in diameter from 12 to 20 mm. In addition to light and image bundles, they contain working channels for suction, air insufflation, and biopsy instruments. These fiberscopes are designed for both diagnostic and therapeutic procedures.

Airway Fiberscopes. The number of accessory components and ultimately the diameter of the fiberscope depend on whether the scope is designed for diagnostic or therapeutic procedures. Bronchoscopes with an external diameter as small as 1.8 mm will easily pass through a tracheal tube of 2.5 mm inner diameter. Because a fiberscope this small, however, has no directional control apparatus or working channel, it is suitable for diagnostic purposes only. As a directional control system and working channel are added, the diameter of the fiberscope increases. The 2.2-mm-diameter scope is designed for use in pediatric patients; this fiberscope has directional control, but no working channel. The standard adult flexible fiberoptic laryngoscopes such as the Olympus LF-2 (4.0 mm diameter) or Pentax FI-10P (3.5 mm diameter) contain light and image



Fig. 9. Fiberoptic light sources: Top halogen, Bottom xenon.

bundles, two-way directional control, and one working channel. Flexible fiberoptic bronchoscopes are 5–6 mm in diameter and feature larger fiberoptic bundles and working channels than laryngoscopes. These bronchoscopes are quite suitable for fiberoptically assisted tracheal intubation of adults (Table).

Maintenance of Flexible Fiberscopes

Although modern fiberscopes are flexible, excessive bending and angulation will fracture the

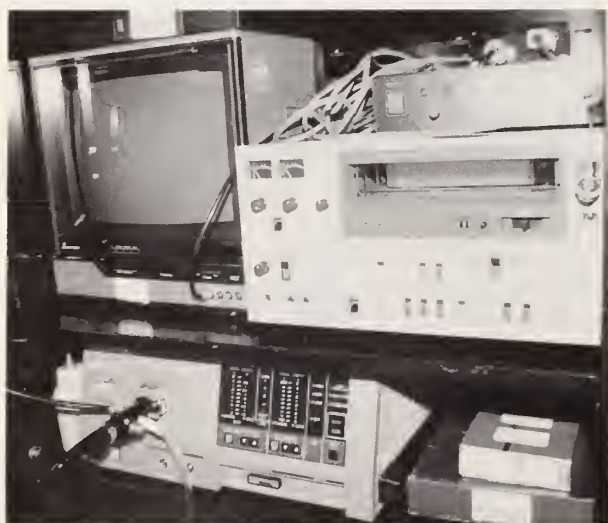


Fig. 10. Complete fiberoptic video system with light source, video monitor, and videotape machine.

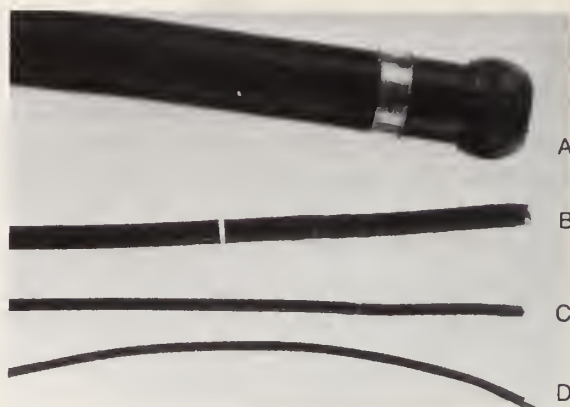


Fig. 11. Distal ends of four different fiberscopes. As more channels are added, diameter of scope increases. A, colonoscope, 15 mm diameter; B, laryngoscope, 4 mm diameter; C, pediatric laryngoscope, 2.2 mm diameter, two-way directional control but no working channel; D, ultrathin bronchoscope, no working channel and no directional control. *Reproduced with permission from Dierdorf SF. Types and physics of fiberscopes. Anesth Clin North Am 1991; 9(1):19–34.*

fiberoptic bundles. Breakage of fiber bundles is a frequent and serious problem. Broken fiberoptic image bundles appear as black dots in the visual field. A few broken bundles do not interfere with laryngoscopy. However, a large number of broken bundles in the center of the fiberscope seriously hampers visibility. Common causes of broken bundles include closing the storage case on the insertion cord and biting the insertion cord. Repair of broken cords is expensive. Fiberscopes should be stored in the extended position, in cabinets or plastic tubes rather than storage cases. A bite block should be inserted in the mouth of awake patients to prevent them from biting the insertion cord. Modern fiberoptic laryngoscopes are durable and will provide years of satisfactory service if simple precautions are taken to prevent fiber breakage.

Cleaning and disinfection of fiberscopes is not standardized. There are no definitive prospective studies that dictate how fiberscopes should be decontaminated. It is estimated that over 8 million fiberoptic gastrointestinal endoscopies and over a half million fiberoptic bronchoscopies are performed annually in the United States. A review of the medical literature has revealed 281 infections transmitted by gastrointestinal endoscopy and 96 infections transmitted by bronchoscopy (10). Common organisms transmitted via gastrointestinal endoscopy include hepatitis B virus, *Salmonella*, and *Pseudomonas*. Organisms transmitted via bronchoscopy include *Pseudomonas* and mycobacteria (tuberculosis). The most commonly recommended disinfecting agent for flexible fiberoptic endoscopes is 2% glutaralde-

TABLE
Specifications of Common Flexible Fiberoptic Laryngoscopes and Bronchoscopes

Manufacturer	Olympus	Pentax	Olympus	Pentax
Model	LF-2	FI-10P	BF-10	FB-19H
Type of scope	Laryngoscope	Laryngoscope	Bronchoscope	Bronchoscope
External diameter (mm)	4.0	3.5	6.0	6.3
Angle of view (degrees)	75	90	100	90
Range of tip deflection (degrees)	Up to 120 Down 120	Up to 130 Down 130	Up to 160 Down 130	Up to 160 Down 100
Working length (cm)	60	60	55	55

In 1993 scopes ranged in price from about \$8,000 to \$12,000.

hyde; however, exposure time is controversial and not standardized.

The Working Party of the British Thoracic Society published guidelines for prevention of cross-contamination of bronchoscopes in 1989 (11), including the following procedures:

- bronchoscope should be cleaned and disinfected at the beginning of the first procedure of the day and immediately after each procedure
- after the valve is dismantled, all parts of the bronchoscope should be washed and brushed in neutral detergent
- after each procedure, the bronchoscope should be soaked in 2% glutaraldehyde for 20 min (bronchoscopes should be washed before disinfection because glutaraldehyde can act as a fixative for mucus and blood)
- after the glutaraldehyde soak, the channel should be rinsed with sterile water or 70% alcohol but not with tap water
- before bronchoscopy is performed in an immunocompromised patient, the bronchoscope should be cleaned and disinfected as usual, except that the glutaraldehyde soak should be continued for 60 min
- nonimmersible bronchoscopes should be phased out
- if effective cleaning and disinfection is achieved, dedicated bronchoscopes for high-risk patients are unnecessary

Since there are no universally accepted guidelines for disinfection of flexible fiberoptic endoscopes, each department that uses fiberoptic endoscopes should develop a disinfection protocol in conjunction with the hospital's Infection Control Committee. Some important principles of disinfection need to be considered when developing a disinfection protocol. Thorough cleaning of the instrument with a detergent to remove debris (blood, mucus) prior to disinfection is essential; residual blood or mucus may contain infective organisms embedded in the debris that remain viable after soaking in disinfectant solution. *Mycobacterium tuberculosis*, the most likely airway

organism, which is resistant to disinfection, is effectively neutralized by soaking the instrument in glutaraldehyde for 20 min (12). Although the likelihood of transmitting infectious disease via a flexible fiberoptic laryngoscope or bronchoscope is low, the consequences of such an infection are great. Disinfection protocols must be strictly observed.

Summary

An understanding of how the flexible fiberoptic scope is constructed and how the various components function enhances the endoscopist's skills of scope manipulation while avoiding damage to the fiberscope.

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Preparation for Intubation of the Awake Patient

ALLAN P. REED, M.D.

PATIENTS coming to surgery and anesthesia share certain fears, some valid and some without foundation. Among the concerns they express preoperatively is the expectation of perioperative pain (1). For this reason, patients usually prefer general anesthesia (1), which they anticipate will guard against physical and emotional suffering. A physician's recommendation for awake intubation is the partial realization of the patient's worst fears. Each patient must understand the unique circumstances requiring awake intubation and must be assured of the increased margin of safety offered by its use. Physicians and patients benefit from detailed discussions of specific indications for awake intubation, as well as possible adverse consequences. Those at increased risk for airway obstruction, hypoxemia, upper airway trauma, cervical spinal cord damage, and/or dental damage generally comprehend the need for awake intubation and consent (2, 3), despite understandable reservations. Those motivated by an appreciation of the dangers associated with intubation under general anesthesia tend to cooperate better during the procedure and harbor less ill-will afterward. The common indications for awake intubation are outlined in Table 1.

Premedication

The preoperative goal is to achieve anxiolysis (7). Fostering a good doctor-patient relationship is the best method of preventing preoperative ter-

rors (8). Patients who develop trust in their physician's expertise and caring personality tend to be more relaxed. Therefore, the preanesthetic interview provides an opportunity not only to comprehend the patient's physiologic requirements, but also to establish the personal interaction that can flourish in a strong doctor-patient relationship. The interview must be conducted in a sincere and unhurried manner. Matters that are routine to the physician are unique and often overwhelming to many patients. The investment of time in a professional relationship pays premiums in patient acceptance and cooperation later (9).

Despite all efforts at discussion, as patients progress toward the operating room, anxiety sometimes degenerates into terror. Prior administration of sedatives is a humane attempt at mitigating the horrors experienced prior to surgery.

Although the patient's emotional preparation requires personal interactions, physiologic preparation relies on judicious use of medications. Several drugs can be employed, but one concept remains inviolate: Dry the airway (10). Copious airway secretions pose a dual problem. Secretions further obscure an already limited view through the fibroscope. Although various suctioning maneuvers usually restore the view, elimination or reduction of this impediment facilitates intubation. Furthermore, awake intubation requires use of topical local anesthetics. For these agents to work effectively, they must actually contact the mucosa. An intervening layer of secretions prevents local anesthetics from reaching the intended areas, resulting in failed sensory blockade (11). Moreover, copious secretions could wash local anesthetics away from a particular site, thereby severely limiting their duration of action. Topical local anesthetics applied to the airway

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are of varying benefit when antisialogogue premedication is withheld (12).

The antisialogogues commonly employed in clinical practice are atropine, glycopyrrolate, and scopolamine (Table 2). Antisialogogues prevent additional discharge of secretions, but they do not eradicate secretions that have already collected. Therefore, even a rapid-acting medication such as atropine must be administered sufficiently far in advance to retard further collections and to provide for elimination of previous collections. Antisialogogues are typically administered parenterally and are optimally received approximately 1½–2 hr prior to application of topical local anesthetics (13).

One of the most important side effects of antisialogogue use is arrhythmias. Since arrhythmias are most likely to occur following intravenous administration, it is advisable to give them intramuscularly, subcutaneously, or by mouth. Although scopolamine offers the additional benefits of added amnesia and sedation, its use is limited by a predilection toward delirium. Other premedications include benzodiazepines, butyrophenones, and narcotics. Patients with significant airway compromise often require conscious muscle tone to maintain airway patency. Sedating such patients in the nursing unit may seriously jeopardize their ability to oxygenate and ventilate. Airway collapse may occur when they are unmonitored and are alone in their rooms or in an elevator while attended by unskilled paramedical personnel. Under such

conditions, institution of prompt, lifesaving treatment is unlikely. Consequently, those patients with severe airway disease should receive only atropine or glycopyrrolate premedication. Additional medications can be administered cautiously under close supervision in the operating room.

Sedation

Monitoring devices are applied and venous access is secured in the operating room. Monitoring generally consists of measurement of blood pressure, pulse, and respiratory rate, as well as observation of cardiac rhythm on an electrocardiographic display and oxygen saturation on a pulse oximeter. Procedures that depend on patient cooperation, such as gargling with 4% lidocaine, are accomplished before the administration of intravenous sedatives because the partially sedated patient may be unable to comply with instructions to gargle and expectorate. Even worse, the sedated patient might aspirate. The primary goal of sedation during awake intubation is anxiolysis. Secondary goals include maintenance of spontaneous respiration, adequate oxygenation, and sufficient ventilation. The patient's ability to inspire deeply on command facilitates ventilation and oxygenation and helps to align the vocal cords, larynx, and fiberscope. A tertiary consideration is amnesia of potentially uncomfortable procedures, which is desirable for the patient's psychologic outlook toward repeat awake intubations and other medical care. Lingering negative recall of previous medically related experiences can create sufficient anxiety about upcoming events to dissuade patients from accepting further medical care. Induction of amnesia under these circumstances represents a sympathetic attempt to prevent overwhelming anxiety from entering into further decision-making processes. It is not an effort to hide information from the patient.

Narcotics, benzodiazepines, and butyrophenones are most commonly used to achieve these goals. Ketamine is rarely employed for this purpose because of its associated copious secretions and postoperative hallucinations. The benzodiazepines' rapid onset of sedation and anterograde amnesia make them a desirable option for awake intubations (14, 15). The most popular benzodiazepines are midazolam, diazepam, and lorazepam. Although lorazepam provides the most profound sedating and amnestic properties, it is difficult to use owing to its relatively long onset time, 5–20 min (Table 3). Midazolam and diazepam, with on-

TABLE 1
Indications for Intubation of the Awake Patient

History of difficult intubation	Trismus due to mechanical problems
Large tongue (Mallampati/Samsoon class IV) (4, 5)	Unstable cervical vertebrae
Micrognathia	Trauma
Protruding maxillary incisors	Face
Short muscular or obese neck	Small mouth opening
Decreased temporomandibular joint range of motion	Hematomas
Combinations of the above five characteristics (6)	Lacerations
Decreased range of motion of cervical vertebrae	Upper Airway
Prominent maxilla	Hematomas
Microsomia	Lacerations
Hoarseness and rheumatoid arthritis	Cervical spine
Thyromandibular distance	Instability
Laryngeal tilt	Congenital airway abnormalities
	Large fixed tongue
	Clefts
	Upper airway tumors
	Cysts
	Hygromas
	Cancers

TABLE 2
Antisialagogues in Common Clinical Use

Agent	Dose (mg)	Onset	Duration	Side effects
Atropine	0.4–0.8 IV, IM, SQ, PO	IV rapid IM, SQ, PO 1–2 hr	IM, SQ, PO 4 hr	Tachyarrhythmias, PVCs Urinary retention Decreased GI motility Hyperthermia Delirium
Glycopyrrolate	0.1–0.2 IV, IM, SQ 1–2 PO	IV 1–4 min IM, SQ 20–40 min PO 1 hr	IV 2–4 hr IM, SQ 4–6 hr PO 6 hr	Tachyarrhythmias, PVCs Urinary retention Decreased GI motility Delirium or excitement
Scopolamine	0.3–0.6 IV, IM, SQ	IV 1 min		Tachyarrhythmias Hyperthermia Amnesia Sedation

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set times of three minutes or less, are both easier to use than lorazepam. Regardless of the specific drug selected, small incremental doses are administered until a sedated but cooperative state has been achieved. The interval between successive doses should be at least equivalent to the drug's maximal onset time. Otherwise, the patient soon becomes oversedated, uncooperative, and apneic. Midazolam is supplied as a water-soluble compound, but diazepam is prepared in a propylene glycol (17) and benzoic acid formulation, which frequently produces a burning sensation on injection and causes irritation of endothelial linings, which predisposes to thrombosis. The burning sensation can be prevented by mixing lidocaine with diazepam before injection.

Butyrophenones sometimes replace benzodiazepines, although the two classes of agents are not pharmacologically equivalent. Droperidol, which is classically selected for this purpose, has the unusual effect of permitting the patient to tolerate painful procedures without recoiling from noxious stimuli. Contrary to some reports, droperidol is not a good amnestic (21). Patients exposed to painful stimuli while receiving droperidol recall the events clearly. The onset of peak action may require 20 min, predisposing to overdose whenever incremental administration proceeds too rapidly. Side effects include anxiety, restlessness, unusual physical sensations, extrapyramidal signs, and hypotension (22). The onset of extrapyramidal effects may be delayed for 6–12 hr (23). Another beneficial property of droperidol is antiemesis.

Narcotics provide additional sedation, analgesia, and euphoria. They also depress laryngeal reflexes (24). Although all narcotics share these properties, morphine and fentanyl have been

used most often for laryngoscopy of the awake patient. The onset of action of intravenous morphine is approximately 10 min. Fentanyl's onset of action is only two minutes. To hasten an already time-consuming procedure, agents with shorter onset times are desirable. Narcotics generally produce respiratory depression and often result in bradycardia.

Adding narcotics to droperidol creates neuroleptanalgesia, which offers moderate degrees of analgesia, sedation, and cardiovascular stability. Close observation is required to protect from recall, hypoxia, hypercarbia, tachycardia, and hypertension. Achievement of the desired goals requires multiple incremental doses, allowing for the clinical effect of each dose to occur before the next is administered. A combined preparation of fentanyl and droperidol (Innovar) is commercially available, but its exclusive use is ill-advised. Multiple repeat doses of Innovar provide excessive and cumulative amounts of droperidol, which may last for 6–12 hr or more. Fentanyl's actions usually last only one to two hours, depending on multiple factors. Consequently, postoperative patients tend to experience prolonged emergence, dysphoria, and pain following large doses of Innovar. Once an appropriate dose of droperidol is attained, subsequent episodes of pain are best treated solely with narcotics.

When administered individually, neither narcotics nor benzodiazepines produce significant cardiovascular impairment. However, combinations of diazepam and high doses of fentanyl have been shown to produce decreases in myocardial contractility, systemic vascular resistance, heart rate, cardiac output, and hypotension (25–27). Even at moderate and low doses of midazolam and fentanyl, a synergism exists, which potenti-

TABLE 3

Characteristics of Sedatives Commonly Employed for Laryngoscopy and Intubation of the Awake Patient

Sedatives	Pharmacologic actions	Dose	Onset time	Duration	Side effects
Benzodiazepines	Sedation Anterograde amnesia Antiepileptic				
Midazolam		IV, IM 5–7 mg (0.075 mg/kg)	IV 1–3 min (15) IM 15–30 min	IV, IM 2 hr	Respiratory impairment in high doses
Diazepam		IV 2–7 mg (.03–.1 mg/kg) IM Not recommended PO 3–11 mg (.05–.15 mg/kg)	IV <3 min IM 15–30 min PO 30–60 min	IV min-hr (14, 17)	Respiratory impairment in high doses IV and IM injections are painful Thrombophlebitis
Lorazepam		IV, IM, PO 1–4 mg	IV 5–20 min IM 30–120 min PO 60–120 min	IV 4–6 hr IM, PO 8 hr	Respiratory impairment in high doses
Butyrophenones	Sedation Antiemetic (16) Indifference				
Droperidol		IV, IM .625–10.0 mg	IV, IM 5–20 min	IV, IM 6–12 hr (18)	Dysphoria (19) Extrapyramidal symptoms (20) Mild alpha adrenergic antagonist Prolongs emergence from anesthesia
Narcotics	Analgesia Sedation				
Morphine		IV, IM, SQ 2–10 mg	IV 5–10 min IM 30–60 min SQ 30–90 min	1–6 hr	Respiratory depression Bronchospasm Chest wall rigid Bradycardia Vomiting Hypotension Biliary spasm
Fentanyl		IV, IM 50–100 mcg	IV 2 min IM 10–15 min	IV, IM 30–45 min	Similar to morphine; bronchospasm, hypotension, biliary spasm less common

Dosages and times are broadly generalized and may vary widely from patient to patient. Slow, careful titration is required for each patient.

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ates the effects of both drugs (28). Analgesia for intubation of the awake patient is provided with local anesthetics. Consequently, it is unlikely that sufficiently high doses of fentanyl will be required to interact adversely with the cardiovascular system, even in combination with diazepam.

Midazolam was originally thought to be relatively innocuous. However, it has been implicated in over 80 deaths after use for sedation during diagnostic or therapeutic procedures. Opioids had been used concurrently in many of these

cases. Morbidity was associated mostly with spontaneous ventilation in the absence of supplemental oxygen administration. Subsequently, midazolam's respiratory safety has been confirmed at doses of 0.05 mg/kg. Fentanyl 2.0 mg/kg resulted in hypoxemia in half of all patients tested and depression of the CO₂ response curve, but no incidences of apnea. The combination of these two drugs produced hypoxemia in almost all patients and apnea in half of the patients tested without depressing the CO₂ response curve more than that seen with fentanyl alone (29).

TABLE 4
Sensory Innervation of Upper Airway Segments

Structure	Innervation (cranial nerve no.)
Nose	Trigeminal (V)
Tongue	
Anterior	Lingual (V)
Posterior	Glossopharyngeal (IX)
Pharynx	Glossopharyngeal (IX) Vagus (X)
Upper larynx	Superior laryngeal (X)
Vocal cords	Recurrent laryngeal (X)
Trachea	Vagus (X)

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Airway Anesthesia

Airway instrumentation may result in convulsant withdrawal, projectile vomiting, or ferocious coughing, any one of which will prevent successful laryngoscopy and intubation. Therefore, a plan for blocking sensory input from the airway must be devised. To accomplish this task in a logical manner requires understanding the sensory innervation of the upper airway.

The upper airway begins simultaneously at both nose and mouth (Table 4). Afferent input from the nose is carried by the trigeminal nerve (V). Sensation from the tongue is divided between two nerves. The lingual nerve (V) supplies the anterior tongue, and the glossopharyngeal nerve (IX) supplies the posterior tongue. The pharynx receives sensory input from the glossopharyngeal nerve (IX) and the vagus nerve (X), and the upper larynx is supplied by the superior laryngeal nerve (X). Both the vocal cords and lower larynx receive afferents from the recurrent laryngeal nerve (X). Finally, the trachea is supplied by the vagus nerve (X).

The superior laryngeal nerve actually divides into an internal and external branch. The internal branch supplies sensory innervation from the inferior aspect of the epiglottis down to (but excluding) the vocal cords (30). The segment is called the upper larynx. This branch also sends afferent fibers to the most proximal portions of the hypopharynx (31). The external branch supplies only motor innervation to only one muscle, the cricothyroid muscle (32, 33). The recurrent laryngeal nerve carries both sensory and motor fibers. The sensory portion of this nerve is distributed to the vocal cords, lower larynx, and trachea. Its motor contributions go to all the laryngeal muscles except the cricothyroid muscle (34) (Table 5).

TABLE 5
Innervation of the Larynx

Nerve	Function
Superior laryngeal (vagus)	
Internal branch	Sensory from inferior aspect of epiglottis to (but excluding) vocal cords (upper larynx)
External branch	Motor to cricothyroid muscle
Recurrent laryngeal (vagus)	Sensory from vocal cords to lower larynx and trachea Motor to all laryngeal muscles except cricothyroid

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Sensory innervation of the upper airway is mediated by cranial nerves and their branches. Unlike major conduction anesthesia or perivascular anesthesia, upper airway anesthesia cannot be accomplished from one central needle location. In fact, the cranial nerves that supply the airway are extremely difficult to anesthetize individually.

Four major categories of safe techniques for upper airway anesthesia exist: topical local anesthetics, topical vasoconstrictors, superior laryngeal nerve blocks, and transtracheal blocks.

Topical Local Anesthetics. Topical local anesthetics are highly versatile and can be administered to either all or part of the airway. Nebulized 4% lidocaine easily and successfully anesthetizes the entire airway. Simply place 4 mL of 4% lidocaine into a nebulizer, flow oxygen through the nebulizer, and channel the nebulized lidocaine through a face mask. Preformed holes in the plastic face mask should be covered with tape

TABLE 6
Comparison of Topical Lidocaine and Benzocaine

	Lidocaine	Benzocaine
Concentration employed	4%	14%–20%
Maximum recommended dose	4 mg · kg ⁻¹	?15–25? mg · kg ⁻¹
Metabolism	hepatic	Plasma ester hydrolysis
Onset	1–5 min	15–30 sec
Duration	1 hr	5–10 min
Time to peak plasma levels after application to larynx	15 min	?
Allergenicity	none	high
Methemoglobin production	none	significant amounts

and the mask fitted tightly to the face to prevent escape of nebulized lidocaine from the system. Instruct the patient to take deep breaths of the solution flowing through the oxygen mask. The nebulized lidocaine method is sufficiently effective to reduce the increases in heart rate and blood pressure that result from endotracheal intubation (35, 36). Furthermore, this method prevents increases in intraocular pressure following laryngoscopy and intubation (37). Although capable of producing profound anesthesia of the airway, inhalation of nebulized lidocaine usually requires 20 min or more to properly prepare the patient.

Alternatively, the anterior tongue, posterior tongue, and pharynx are anesthetized with 4% lidocaine administered by atomizer. Atomized lidocaine can be introduced deeper into the airway by administration of each puff during a vital capacity inspiration. In fact, it is possible to anesthetize the entire airway utilizing atomized 4% lidocaine or a similar agent.

Healthy children, especially those between six and seven years of age, react adversely to local anesthetic sprayed into the larynx. Children are prone to severe bradycardia following this maneuver. Although preoperative intramuscular vagolytics do not protect against bradycardia, intravenous atropine and glycopyrrolate successfully block heart rate decreases under such circumstances (38).

Topical local anesthetics necessitate employing high concentrations, which frequently travel to alveoli where absorption is rapid (39). Despite rapid absorption from alveoli, aerosolized lidocaine 4 mg/kg does not even produce a therapeutic blood level (1–5 $\mu\text{g/mL}$) (40). Consequently, the likelihood of lidocaine toxicity at the 160-mg dose of nebulized lidocaine is low.

Anesthetic effects of topical lidocaine may last up to one hour (41). Onset time is between one and five minutes (42, 43).

Alternatives to topical lidocaine include tetracaine, prilocaine, and benzocaine. Topical tetracaine is no longer recommended for total airway anesthesia because of its narrow margin of safety. The relatively large amounts of topical tetracaine required for total airway anesthesia are associated with toxic reactions. Topical prilocaine and benzocaine provide rapid onset and profound anesthesia, but they also produce significant methemoglobinemia. Pulse oximeters, which are used to guard against hypoxemia, overestimate oxygen saturation (S_{pO_2}) in the face of methemoglobinemia (44). Prilocaine and benzocaine are not only dangerous at the time of ad-

ministration, but they continue to produce escalating levels of methemoglobinemia for up to six hours (44). Benzocaine is metabolized to para-aminobenzoic acid, a highly allergenic molecule. Table 6 compares the advantages and disadvantages of topical lidocaine and benzocaine.

Vasoconstriction of the Nasal Mucosa. Instrumentation of the nose, including passage of an endotracheal tube, fiberscope, or suction catheter, predisposes to epistaxis. Even oral intubation may cause epistaxis if laryngeal secretions must be suctioned through the nose. Once epistaxis occurs, visualization becomes impaired. Consequently, vasoconstriction of the nose should be considered regardless of the intubation route intended.

Vasoconstriction of the nose is generally achieved with either cocaine or phenylephrine. For this purpose, cocaine has traditionally been used in concentrations as low as 4% and as high as 10%. Recent evidence suggests that 10% cocaine is associated with coronary artery vasoconstriction, diminished coronary blood flow, and an increase in myocardial oxygen demand (45, 46). Because the potential risk of side effects is related to plasma levels, substitution of 4% cocaine for 10% cocaine should diminish the incidence of untoward reactions. Nevertheless, a small segment of the population is especially susceptible to cocaine toxicity because of impaired ability to hydrolyze the drug. Cocaine is degraded by serum cholinesterase and the breakdown products are excreted in the urine. Quantitative or qualitative cholinesterase problems can impair cocaine metabolism, thereby effectively increasing plasma levels (47). Although cocaine can be sprayed into the nose, application by cotton pledgets probably prevents excess absorption by limiting the amount that actually reaches alveoli (48). Nevertheless, direct absorption from the nasal mucosa remains a theoretic possibility (49). Cocaine-soaked cotton pledgets are introduced into both nares and then advanced slowly into the pharynx. Best results are obtained when pledgets remain in place for 10 min.

Phenylephrine is another commonly employed vasoconstrictor. It can be applied in concentrations ranging from 0.25% to 0.5% (50). Although generally not commercially available, 0.5% phenylephrine solutions are readily formulated in any hospital. Phenylephrine is frequently supplied as a 1.0% solution. Simply add 1 mL of 1.0% phenylephrine to 1 mL of 4% lidocaine to manufacture the proper concentration of phenylephrine. Soak cotton pledgets in this solution, introduce them into both nares, and advance them

into the pharynx just as described for the cocaine solutions.

Alternatively, oxymetazoline, a pure alpha-adrenergic agonist that produces vasoconstriction of the nasal mucosa, can be substituted to help prevent epistaxis. It is not a controlled substance and therefore does not require the strict record keeping associated with use of cocaine. Oxymetazoline does not reduce catecholamine reuptake and therefore is devoid of euphoric effects as well as arrhythmogenic properties. Oxymetazoline is more effective than 4% lidocaine with 1:100,000 epinephrine or 10% cocaine for preventing epistaxis (51). Therefore, oxymetazoline seems to represent a superior topical vasoconstrictor, which eliminates the theoretic disadvantages of cocaine use. In actuality, side effects related to cotton pledget application of 4% cocaine to the nose seem to be minimal. The disadvantage of oxymetazoline is its lack of local anesthetic properties. When applied topically for vasoconstriction of the nares, oxymetazoline is used in a 0.05% concentration.

Blockade of the Superior Laryngeal Nerve.

The superior laryngeal nerve is a division of the vagus nerve (X). It courses inferiorly in the neck, running medial to the carotid artery. At the level of the hyoid bone, the superior laryngeal nerve dives deep, to pierce the thyrohyoid membrane, which stretches from the hyoid bone to the thyroid cartilage. At about this point the superior laryngeal nerve divides to produce an internal and external branch (52). The internal branch of the superior laryngeal nerve provides sensory innervation to the upper larynx, and the external branch of the superior laryngeal nerve gives off motor fibers to the cricothyroid muscle (32) (Fig. 1).

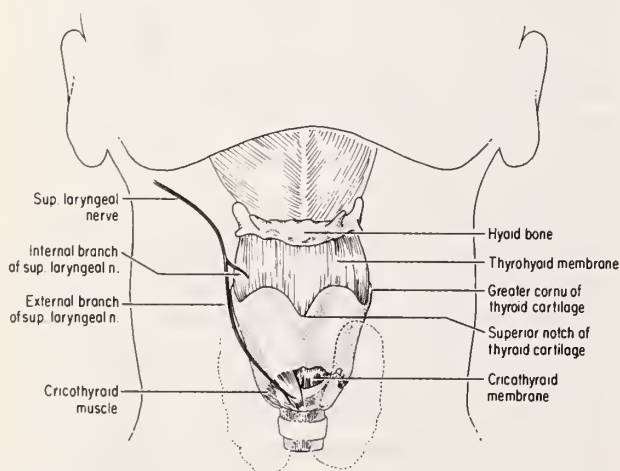


Fig. 1. Anatomy of anterior neck. Adapted from Reed AP, Han DG. Preparation of the patient for awake fiberoptic intubation. *Anesth Clin North Am* 1991; 9(1).

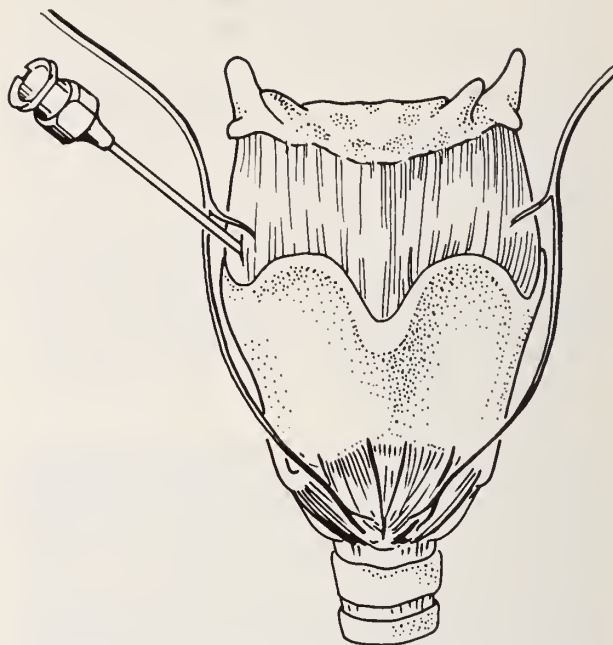


Fig. 2. Needle placement for external approach to superior laryngeal nerve. Adapted from Reed, AP, Han DG. Preparation of the patient for awake fiberoptic intubation. *Anesth Clin North Am* 1991; 9(1).

Sensory interruption of the superior laryngeal nerve is achieved at the level of the thyrohyoid membrane. The patient lies supine with the head extended. Labat's initial description of this nerve block utilized the hyoid bone as the primary landmark (53). Unfortunately, the hyoid bone is difficult or impossible to feel in many patients. Also, it frequently requires deep palpation, which is uncomfortable for most individuals. Consequently, I prefer to employ the thyroid cartilage as the major landmark (54, 55) because it is located more superficially and is more readily identifiable.

The superior notch of the thyroid cartilage, commonly known as the Adam's apple, is the most superficial aspect of the thyroid cartilage and is located in the midline. The superior notch of the thyroid cartilage is palpated and the operator's fingers are moved laterally across the neck until the end of the thyroid cartilage is identified. Prepare the skin over the greater cornu of the thyroid cartilage with isopropyl alcohol. Displace the thyroid cartilage laterally from the opposite side. Take a 3-mL syringe filled with 2 mL of 2% lidocaine and a 25-gauge needle and place the needle through the skin just above the greater cornu of the thyroid cartilage. Once there is resistance to passage of the needle, it lies at the greater cornu of the thyroid cartilage. "Walk" the needle off the greater cornu, in a superior direction. This places the needle between the greater

cornu of the thyroid cartilage and the hyoid bone, the area through which the superior laryngeal nerve courses (Fig. 2). If an aspiration test does not yield blood or air, inject 2 mL of 2% lidocaine without epinephrine. Repeat this procedure on the opposite side. Depending on the relative positions of nerve and needle, the superior laryngeal nerve block may require 5–10 min for onset. To conserve time, perform this block first and attend to other matters while it is setting up. Its duration of action appears to be four to six hours when 2% lidocaine is used (54).

Another option is to perform superior laryngeal nerve blocks from the internal approach. A gauze sponge is soaked in 4% lidocaine and held with a Krause forceps. Have the patient open his or her mouth as wide as possible. Place the lidocaine-soaked sponge into the piriform fossa and hold it there for five minutes by the clock. This must be performed on both sides. The internal approach requires a minimum of 10 minutes and is applicable only to those patients who can open their mouths sufficiently wide.

Although originally designed as a treatment for painful laryngeal problems (56), the superior laryngeal nerve block has found application providing analgesia for awake instrumentation of the airway during bronchoscopy, esophagoscopy, tracheal suctioning, and tracheal intubation (31, 55–57).

Most recently, superior laryngeal nerve block has been employed to facilitate passage of a transesophageal echocardiography probe in the awake patient (56, 58). Whenever topical anesthesia to the upper larynx is inadequate, superior laryngeal nerve block improves patient comfort, reduces the total dose of topical local anesthetic required, and reduces the time required to successfully manipulate the upper larynx (31).

Side effects of superior laryngeal nerve blocks are few. The most important potential complication is hematoma formation, which may arise from needle trauma to the superior laryngeal artery, which courses with the internal branch of the superior laryngeal nerve as it pierces the thyrohyoid membrane. The bleeding, when it occurs, is readily controlled with manual pressure over the site in question (54). The close proximity of the superior laryngeal nerve and artery underscores the importance of careful aspiration prior to injection of local anesthetic (32, 59). Other potential complications include needle penetration of the pharynx and needle plugging by cartilage (55). Local infection and tumor are the only contraindications to this block (59).

The external branch of the superior laryn-

geal nerve serves to tense the vocal cords. Simultaneous blockade of the external branch of the superior laryngeal nerve could theoretically result in difficulty speaking (32).

Transtracheal Blocks. Transtracheal blocks furnish anesthesia of the vocal cords and trachea. This method has enjoyed widespread use and is easily performed. Permit the patient to lie supine with the head extended. Locate the superior notch of the thyroid cartilage, the Adam's apple, and run a finger inferiorly until a depression and another firm structure are appreciated. This depression is the cricothyroid groove and the firm substance is the cricoid cartilage. A membrane, called the cricothyroid membrane, runs from the cricoid cartilage across the groove to the thyroid cartilage (Fig. 1). Identify the cricothyroid groove and prepare the skin overlying it with isopropyl alcohol. Utilize a 3-mL syringe with 2 mL of 2% lidocaine and a 22-gauge needle. Insert the needle through the skin overlying the cricothyroid membrane and direct it posteriorly until the cricothyroid membrane is pierced. At this point, the needle bevel should reside within the trachea (Fig. 3). To confirm its proper location, simply aspirate air through the syringe. Warn the patient to expect vigorous coughing and then rapidly inject the 2 mL of 2% lidocaine. Remove the needle immediately following injection. Coughing helps to spread the local anesthetic along the trachea and up against the inferior aspect of the vocal cords, thereby providing topical anesthesia to all these structures (2). Significant amounts of local anesthetic also reach the alveoli where it is rapidly absorbed. Successful transtracheal block is probably due to both topical anesthesia and systemic absorption. Employing transtracheal blockade in the patient with a full stomach remains controversial. Its merits must be individualized for each patient. Successful transtracheal block prevents coughing and expulsion of aspirated materials (60). Retained vocal cord and tracheal reflexes may jeopardize awake intubation.

Transtracheal block is minimally invasive and is associated with certain complications. Choking or gagging accompanies virtually all transtracheal blocks and is an anticipated side effect, not a complication of the procedure. Approximately 4% of blocks fail to produce adequate vocal cord anesthesia (61). To improve sensory blockade, simply spray additional 4% lidocaine onto the vocal cords under direct vision.

If a traditional hand-held retraction-blade laryngoscope is being used, lidocaine is administered with an atomizer. If a fibroscope is being used, then simply inject 1–2 mL of 4% lidocaine

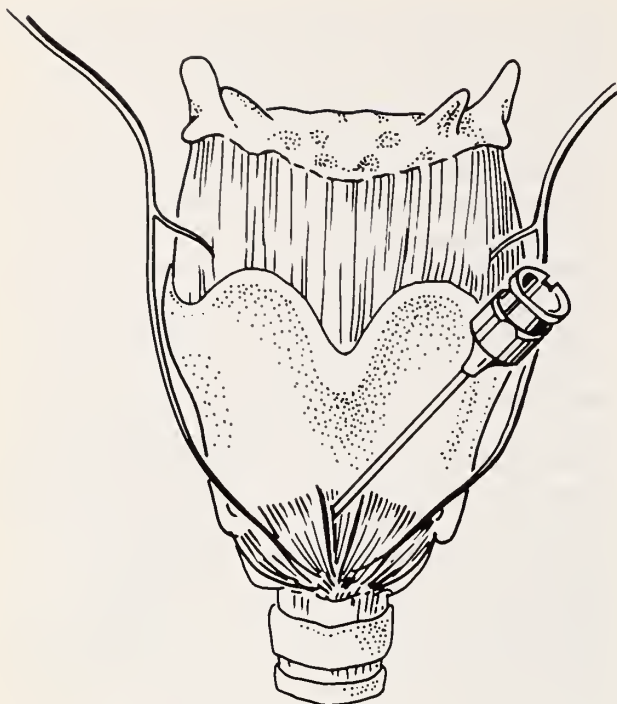


Fig. 3. Needle placement for transtracheal block. Adapted from Reed AP, Han DG. Preparation of the patient for awake fiberoptic intubation. *Anesth Clin North Am* 1991; 9(1).

through the suction port. Allow several minutes for the lidocaine to take effect and instruct the patient to inspire deeply. As this is accomplished, the anesthetized vocal cords will abduct, allowing passage of the fiberscope or endotracheal tube.

Injection of local anesthetic into the trachea allows much of the solution to flow into the lungs where alveolar absorption is rapid. Mechanical problems from needle placement are uncommon (61). Although needles may break in the neck (62), I have never seen this problem using 22-gauge needles. Puncture of the esophagus or other soft tissues has not led to problems. Hematoma formation from laceration of an aberrant artery which occasionally traverses the cricothyroid membrane is rare. Tracheocutaneous fistula formation is also extremely rare (61).

Reflexes produce violent responses to invasion of the airway by foreign bodies. Airway manipulations evoke coughing, vocal cord closure, withdrawal, and vomiting, each of which can hinder laryngoscopy and intubation. Traditional rigid laryngoscopy results in hypertension and tachycardia, and a correctly placed endotracheal tube predisposes to bronchoconstriction (63). In the absence of deep general anesthesia, no amount of sedation can prevent these reactions to airway stimulation. Only profound sensory blockade will offer conditions conducive to awake la-

ryngoscopy and intubation. Awake intubation executed under successful airway anesthesia induces an average mean arterial pressure increase of 10 mmHg and a heart rate increase of 14 beats/min (64).

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Use of the Flexible Fiberoptic Laryngoscope

STEPHEN F. DIERDORF, M.D.

TRACHEAL INTUBATION is routinely performed for most patients undergoing general anesthesia. In the past 20 years, an increased percentage of operations requiring general anesthesia have employed tracheal intubation. Routine tracheal intubation in conjunction with improved intraoperative monitoring has resulted in increased patient safety during general anesthesia. As the safety of anesthesia has increased, it has become evident that one of the most significant causes of anesthesia-related morbidity and mortality is the inability to ventilate patients who are unconscious or paralyzed. In most circumstances, rigid direct laryngoscopy and tracheal intubation can be performed rapidly and atraumatically. However, patients who have either congenital or acquired anatomic abnormalities of the upper airway may not be suitable candidates for standard laryngoscopy techniques. Many alternative methods of tracheal intubation have been developed for patients with "difficult" airways, but these techniques can be unreliable and produce considerable trauma to the upper airway, complicating subsequent attempts at tracheal intubation. Rigid direct laryngoscopy requires alignment of the oral cavity, pharynx, and glottic inlet axes, in order to visualize the larynx and permit endotracheal intubation. In contrast, the flexible fiberoptic laryngoscope conforms to the patient's specific airway contour and does not require axial alignment for visualization of the laryngeal inlet. The fiberscope in many instances permits rapid and safe tracheal intubation of pa-

tients with extremely abnormal upper airway anatomy.

Patients with obvious upper airway abnormalities are ideally detected during the preoperative evaluation (1, 2). Appropriate preoperative planning, employing awake, spontaneously breathing intubation under topical anesthesia, poses little risk to the patient. However, on occasion, even the experienced anesthesiologist cannot discern potential impedance to tracheal intubation and may proceed with general anesthesia, only to discover after induction that the patient cannot be intubated with conventional techniques. Repeated attempts at rigid direct laryngoscopy produce trauma to the upper airway and edema of pharyngeal soft tissues, resulting in an inability to ventilate the patient via face mask. This clinical situation of poor ventilation and inability to intubate the patient's trachea is likely to produce severe hypoxia with resultant permanent neurologic damage or death.

The flexible fiberoptic laryngoscope is a versatile instrument that can provide a mechanism for tracheal intubation of the awake or anesthetized patient. In addition, the fiberscope can be used to assist in the intraoperative positioning of tracheal or endobronchial tubes. An anesthesiologist completing residency training in the 1990s should be skilled in the use of the flexible fiberoptic laryngoscope. For those anesthesiologists not familiar with the technique, this article presents a method for learning to perform fiberoptic laryngoscopy (3).

Recognition of Anatomic Landmarks

One of the most important aspects of learning fiberoptic laryngoscopy is recognition of anatomic landmarks. A methodical approach to identifica-

From the Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana. Address reprint requests to the author, Professor of Anesthesiology, Indiana University School of Medicine, 1120 South Drive, Fesler Hall 204, Indianapolis, IN 46202-5115.

tion of these landmarks contributes to repeated success. Blind passage of the fiberoptic with the hope of suddenly visualizing the glottic inlet is not a reliable technique.

Manipulation of the Fiberscope

Learning how to manipulate the fiberscope is the most important function to be mastered. Skillful manipulation contributes to a high success rate for fiberoptic laryngoscopy and tracheal intubation. When the endoscopist can competently manipulate the fiberscope tip, he or she is able to negotiate most upper airway anatomic abnormalities.

The initial phase of learning is to observe the movements of the top of the endoscope as the control lever is deflected and the body of the scope is rotated in concert with tip deflection. The field of view is a circle that can be divided into four quadrants. If the tip is deflected "up" and the fiberscope rotated clockwise, the upper right quadrant is visualized. In a similar manner, the other three quadrants can also be targeted (Fig. 1).

After formulating a mental image of how the fiberscope moves, the endoscopist can practice fiberscope manipulation with cylindrical models (corrugated breathing tubes, large-bore syringes) while viewing the target through the ocular lens. If at any time the beginner is uncertain about the position of the fiberscope, it is possible to observe the scope directly. After confidence is gained in these preliminary trials, fiberoptic intubation of manikins should then be undertaken. Most beginning endoscopists will accomplish this with relative ease and reliability.



Fig. 1. Fiberoptic scope (left) is held in dominant hand; tip deflector lever is controlled with thumb. Rotation of scope body to right (clockwise) or left (counterclockwise) in conjunction with tip deflection permits viewing of all four quadrants in visual field (right).

Once these goals are achieved, the neophyte is ready to begin fiberoptic laryngoscopy, under supervision, in patients who require general anesthesia. Fiberoptic laryngoscopy in this situation differs considerably from intubation of a manikin. Initial attempts at patient intubation are likely to be unsuccessful and frustrating for the beginner. Patience, perseverance, and continued practice will culminate in mastery of the techniques necessary for fiberoptic laryngoscopy and tracheal intubation.

The use of an oral airway especially designed for fiberoptic laryngoscopy, such as an Ovassapian or Berman intubating airway, may prove valuable when learning fiberoptic laryngoscopy (Fig. 2). These airways are intended to maintain the fiberscope's midline position and direct the scope toward the glottic inlet. Once the technique of fiberoptic laryngoscopy is mastered, these airways are generally not required.

Prior to insertion of the fiberoptic laryngoscope, the tracheal tube is threaded over the scope. If the 15-mm adapter is removed from the tracheal tube, the tube can be secured on the tapered end of the body of the fiberscope. This prevents the tracheal tube from sliding down the insertion cord during laryngoscopy (Fig. 3). Manual extraction of the tongue by an assistant may open the pharyngeal cavity and displace the epiglottis from the back of the pharyngeal wall, thereby exposing the glottic inlet.

Preparation of The Laryngoscope

Easy accessibility of the fiberoptic laryngoscope and its light source increases the likelihood

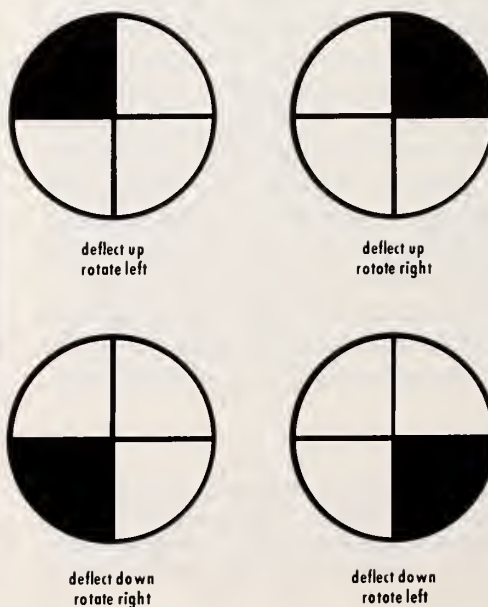




Fig. 2. Left Ovassapian intubating airway. Right Berman intubating airway.

that the instrument will be used and makes the scope readily available for emergent situations. A mobile cart that houses the fiberscope, its light source, airways, tracheal tubes, cleaning solutions, and other necessary supplies facilitates rapid access to the equipment (Fig. 4).

Prior to induction of anesthesia, the fiberscope should be examined to determine that the image viewed is sharp and clear. If the image is blurred, the objective lens should be cleaned with a damp cloth. Printed material can be scanned to determine image clarity (Fig. 5). Adjustment of the focusing ring may improve image quality. Broken fibers appear as black dots in the visual field (Fig. 6). The light source should be activated. The light source is most likely to burn out during the current surge immediately after activation. Evaluation and preparation of the fiberscope prior to induction of anesthesia fosters a trouble-free induction and intubation sequence.

Preparation of the Patient

Initial attempts at fiberoptic intubation are best carried out under supervision in selected healthy nonobese individuals undergoing general anesthesia. In these initial procedures, preoperative administration of an antisialagogue (atropine, glycopyrrolate) may be helpful in reducing pharyngeal secretions. During early attempts, fiberoptic laryngoscopy should be performed via the oral route. Induction of anesthesia can be accomplished with standard induction agents (thiopental, propofol) and muscle relaxants. After an adequate degree of muscle relaxation is achieved, laryngoscopy may begin.

During laryngoscopy the electrocardiograph and pulse oximeter are observed by an assistant. For most normal nonobese patients, three minutes of laryngoscopy can be performed before significant changes occur in hemoglobin saturation. If laryngoscopy is not successful within three minutes, mask ventilation should be performed for one minute to maintain an adequate level of

oxygenation and normocarbica. If muscle relaxation is performed with a nondepolarizing muscle relaxant, several intermittent three-minute periods become available in which to perform laryngoscopy.

A major difference between the awake patient and the anesthetized patient is the degree of tone in the pharyngeal muscles. The patient receiving general anesthesia has little pharyngeal muscle tone and the pharynx appears to be "collapsed" when initially viewed through the fiberscope. Supporting structures of the epiglottis are also relaxed, permitting the epiglottis to fall posteriorly against the posterior pharyngeal wall. Although this loss of muscle tone complicates fiberoptic laryngoscopy, it offers the advantage of requiring much less time for patient preparation than topical anesthesia of the awake patient and provides the ultimate in patient comfort.

Technique for Orotracheal Fiberoptic Laryngoscopy

The fiberscope is introduced 10 cm along the midline of the tongue and pharynx (Fig. 7). The view through the fiberscope is then ascertained. If this view is pink or white, without recognizable landmarks, the fiberscope should be slowly withdrawn until landmarks are identified. When the pharyngeal cavity has been revealed, the fiberscope is slowly advanced until the epiglottis is seen. The fiberscope can then be manipulated under the epiglottis to visualize the glottic inlet. The glottic inlet should be targeted to the center of the visual field. If the glottis appears to "drift" to the periphery, scope advancement should be halted and the tip deflected and rotated so that the glottis is centered. When the glottic inlet is in the center of the visual field, the fiberscope will enter the glottis as the instrument is advanced. The endoscopist must resist the temptation to quickly advance the fiberscope once the glottis appears in the field of view. After the fiberscope enters the trachea, the scope is advanced to a position just



Fig. 3. Tracheal tube threaded on fiberoptic laryngoscope. The 15-mm adapter has been removed from tracheal tube, which is securely attached to tapered body, preventing tube from sliding down scope.

above the carina. Once the fiberscope is positioned in the trachea, the tracheal tube is advanced over the fiberscope and into the trachea. If resistance to passage of the tracheal tube is encountered, the tube should be withdrawn 1–2 cm and rotated 90 degrees toward the patient's midline and then advanced. Resistance is frequently created as the endotracheal tube impacts on the arytenoid cartilage. After passage of the tracheal tube into the trachea, tube position can be confirmed with the fiberscope as the scope is withdrawn.

This method for learning fiberoptic laryngoscopy and tracheal intubation is an efficient and effective technique of mastering endoscopy skills. After the endoscopist can perform oral fiberoptic laryngoscopy, he or she can practice nasotracheal laryngoscopy and intubation in anesthetized patients. Following mastery of these approaches, awake patients are suitable candidates.



Fig. 4. Mobile cart holding fiberscope, light source, and all necessary supplies ensures ready availability for tracheal intubation.

Fiberoptic intubation of the awake patient prepared by topical anesthesia is often easier than intubation of the patient who is under general anesthesia. The most important aspect of intubation of awake patients is profound topical anesthesia. By mastering fiberscope manipulation in patients who have received general anesthesia, the endoscopist can devote more time and attention to achieving adequate topical anesthesia for the awake patient.

Common Problems

A number of problems that complicate fiberoptic laryngoscopy are relatively easy to correct. The flexible fiberoptic laryngoscope should be carefully evaluated prior to every fiberoptic intubation. This evaluation prospectively detects dirty objective lens, unfocused ocular lenses, broken fiber bundles, occluded working channels, and dim light sources. Oropharyngeal secretions may obscure the view when they cover the objective lens. Insufflating oxygen through the working channel at 3–5 L/min will “blow” secretions away from the lens. The cool, dry oxygen will also deter condensation from forming on the lens and prevent fogging. Application of suction to the working channel should be avoided because this may “pull” secretions toward the lens rather than remove them completely, and thus impair the view. Nasopharyngeal or oropharyngeal bleeding from prior attempts at blind nasal intubation may also obscure the view and make fiberoptic laryngoscopy impossible. Blind nasal intubations should be avoided prior to fiberoptic laryngoscopy.

If the view is unrecognizable, the fiberscope should be slowly withdrawn until the endoscopist identifies anatomic landmarks. Blindly passing the fiberscope invariably inserts the fiberscope into the esophagus. The fiberscope should be advanced and withdrawn slowly and deliberately. Rapid insertion of the fiberscope will pass the scope beyond the glottic inlet and into the esophagus.

Resistance to passage of the tracheal tube after the fiberscope has advanced into the trachea is generally caused by impaction on the right arytenoid cartilage. The solution is to withdraw the tracheal tube 1–2 cm, and internally (toward the midline) rotate the tube prior to reinsertion.

Many of the difficulties that complicate fiberoptic endoscopy are overcome with simple solutions. Careful planning and preparation of equipment and patients will easily correct most of these difficulties.

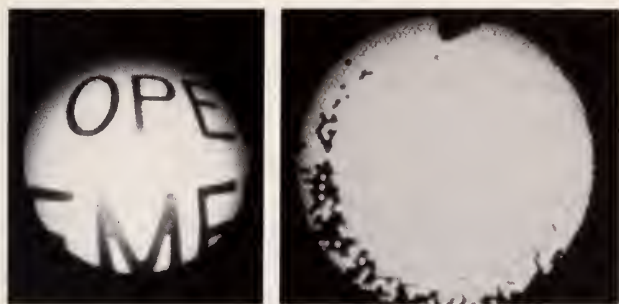


Fig. 5. Left During preparation of fiberscope for laryngoscopy, printed material should appear sharp and clear when viewed through scope. Fig. 6. Right Fiberscope with a large number of broken fibers (each black dot is one broken fiber).

Clinical Indications for Flexible Fiberoptic Intubation

There are several clinical indications for flexible fiberoptic intubation. Clearly, the patient who poses anticipated difficulty in mask ventilation and tracheal intubation requires awake intubation, which is generally performed utilizing a fiberscope. Tracheal intubation of this type of patient has been well documented (4, 5). The key

determinant of success in intubation of the awake patient is preparation and profound airway anesthesia.

In addition to the patient with anticipated difficulty in tracheal intubation, several indications for orotracheal intubation of the anesthetized patient using flexible fiberoptic laryngoscopy exist (6, 7). Patients known to be difficult to intubate with rigid direct laryngoscopy, but also known to be easy to ventilate with a face mask, are excellent candidates for flexible fiberoptic intubation after the induction of anesthesia. Most of these patients can be quickly and easily intubated with the fiberscope. Intubation with this technique is much more comfortable for the patient than an awake tracheal intubation.

One of the most important indications for use of the flexible fiberoptic laryngoscope is the patient with the unanticipated difficult airway. The difficulty with laryngoscopy in this type of patient is usually discovered after anesthesia has been induced. When confronted with this clinical situation, it is best to proceed with flexible fiberoptic intubation rather than repeated attempts at rigid direct laryngoscopy, which may



Fig. 7. Fiberoptic laryngoscope being passed into oropharynx. Scope is held 10 cm from distal end.

produce considerable airway edema, increasing the difficulty of administering positive pressure ventilation by face mask.

Summary

The flexible fiberoptic laryngoscope is an excellent instrument for performing tracheal intubation in patients with abnormal upper airway anatomy. In order to prepare to use the fiberscope for the infrequent patient with a "difficult" airway, the anesthesiologist must initially learn and practice the technique in patients with normal anatomy. Orotracheal intubation with the fiberscope in these patients receiving general anesthesia provides the anesthesiologist with abundant opportunities to become skillful.

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The Unanticipated Difficult Intubation with Adequate Mask Ventilation

ALLAN P. REED, M.D.

NUMEROUS ATTEMPTS have been made to establish criteria for predicting the difficult intubation. No single factor has emerged as a reliable predictor, but some criteria are used to warn of potential difficulty (box) (1).

The incidence of unanticipated difficult intubation approximates one in every 2,230 patients in the general population. In the obstetric population, the incidence is ten times higher (2). Fortunately, most obstetric patients undergo natural childbirth or conduction anesthetics and never require endotracheal intubation.

The most widely quoted recent papers on predicting difficult intubation were written by Mallampati in 1985 and Samssoon in 1987. Both studies related oropharyngeal anatomy to the laryngoscopic view obtained with a Macintosh 3 laryngoscope blade. These investigators agree that the ability to visualize a patient's tonsillar pillars predicts excellent laryngoscopic view of the larynx (2, 3) (Fig. 1). Classes II, III, and IV are not predictive of the difficulty or ease of laryngoscopy; many patients who turn out to be difficult to laryngoscope belong to Samssoon class IV.

In 1992, Roche et al. confirmed that no single factor reliably predicts the difficult intubation. Roche et al. investigated the prognostic importance of the three Samssoon criteria: prominent incisors, micrognathia, and short neck. Although

none of these factors predicted difficulty by itself, combinations of these factors enhanced the reliability of predicting difficulty (4) (Fig. 2).

Retraction Blades. Devices that push the base of the tongue anterior to the line of vision are called retraction blades. Macintosh and Miller blades are two well-known types.

Typically, the unanticipated difficult intubation patient undergoes induction of general anesthesia. After adequate mask ventilation is achieved, a muscle relaxant is administered and laryngoscopy is attempted. In the United States, most anesthesiologists preferentially begin with a Macintosh 3 laryngoscope blade. Macintosh

Traditional Predictors of Difficult Intubation

Trauma

Upper airway

Hematomas

Lacerations

Cervical spine

Instability

Face

Small mouth opening

Hematomas

Lacerations

Congenital airway abnormalities

History of difficult intubation

Trismus due to mechanical problem

Temperomandibular joint ankylosis

Unstable cervical vertebrae

Anticipated difficult intubation

Micrognathia

Short muscular or obese neck

Decreased temperomandibular joint range of motion

Prominent "buck" teeth

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From Reed AP, Han DG. Preparation of the patient for awake fiberoptic intubation. *Anesth Clin North Am* 1991; 9(1):69-81.

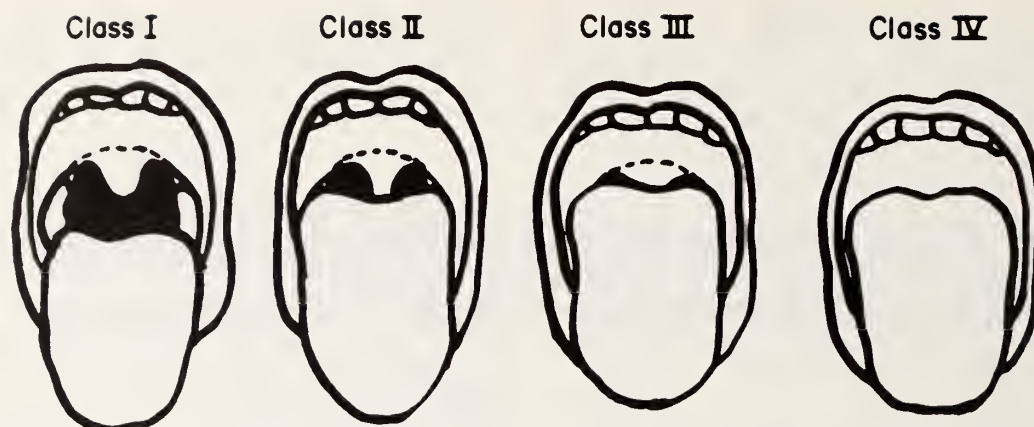


Fig. 1. Samsoon classification. Class I: Tonsillar pillars, uvula, soft palate, hard palate visualized. Class II: Tonsillar pillars not visualized; uvula, soft palate, hard palate visualized. Class III: Base of uvula, soft palate, hard palate visualized. Class IV: Only hard palate visualized. Adapted from ref 2.

blades are placed in the vallecula, with the tip underneath the hyoid bone. Lifting the blade retracts the base of the tongue and pushes the hyoid bone anteriorly. Displacement of the hyoid bone indirectly pulls on various ligaments connecting the hyoid bone to the epiglottis. Thus, the epiglottis is indirectly lifted anterior to the line of vision.

If they fail to lift the epiglottis out of the way with a Macintosh blade, most anesthesiologists advance to a Miller blade, the tip of which is

placed underneath the laryngeal aspect of the epiglottis. Elevating the blade directly pushes the epiglottis out of the line of vision. Prominent incisors often interfere with the use of Miller blades.

In an attempt to visualize the "anterior" larynx, Siker designed a retraction blade with a mirror built into its center (Fig. 3). After the Siker blade is placed in the airway, the larynx is indirectly visualized in the mirror. The endotracheal tube is passed into the airway and manipulated into the larynx as its reflection is watched in the mirror. Although ingenious conceptually, this blade is extremely difficult to use because the mirror reverses right and left. Movements in one direction are seen in the mirror as displacements in the other direction. Use of this blade requires a great deal of practice and development of special skills.

Another variation on this theme is the Bellhouse angulated straight blade (Fig. 4) which represents an attempt to combine the advantages of both Macintosh and Miller (curved and straight) blades. Its distal portion is inserted underneath the epiglottis and directly lifts it out of the line of vision. The angulated (bent) portion facilitates placement in the mouth, while minimizing contact with maxillary incisors. When necessary, an optional prism can be attached to improve visualization of the anterior larynx (5). Prisms allow visualization around the base of the tongue, without the right-to-left shift that accompanies mirror reflections.

The Bullard laryngoscope is a high-tech retraction blade (Fig. 5). It offers a broad retraction blade and does not require sniffing position (6). It is a fiberoptic device and, like all such instru-

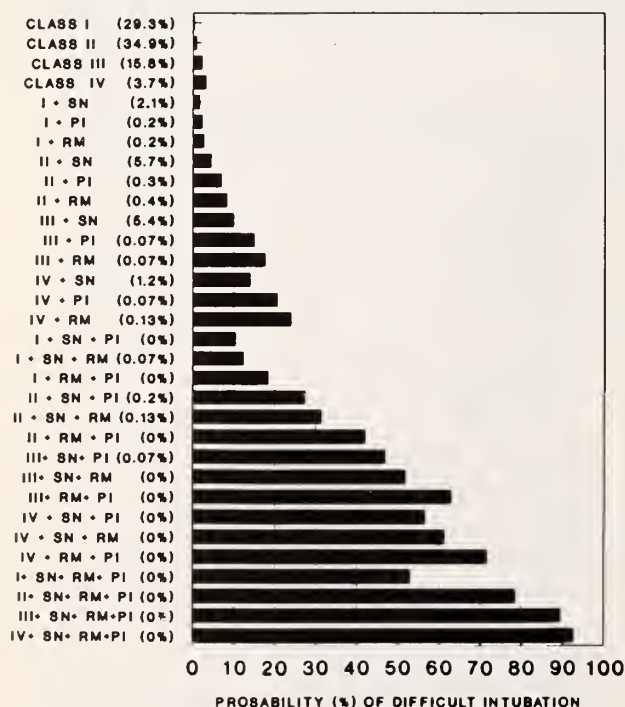


Fig. 2. Probability of experiencing difficult intubation. Class I, II, III, and IV refer to Samsoon classification. SN, short neck; PI, protruding maxillary incisors; RM, receding mandible. Reprinted with permission from ref. 4.

ments, offers a limited field of vision, which is further restricted by blood or secretions in the airway. Sometimes, after visualization of the larynx, it is difficult to advance the endotracheal tube between the vocal cords while using this laryngoscope.

Stylets. Copper wire stylets, slick stylets, and gummed elastic bougies of all kinds have been used in anesthetic practice. Stylets that are lighted (shown in Fig. 6) consist of three parts, a handle, a stylet, and a light bulb. After the stylet's light bulb is illuminated and the room lights are dimmed, the instrument is introduced into the airway and the anesthesiologist observes the light transilluminated through the patient's neck. As the stylet enters the larynx and trachea, the transilluminated light remains bright and well circumscribed. If it enters the esophagus, the light becomes dim and more diffuse (7, 8). This technique entails false positives and false negatives.

Retrograde Techniques. Although far more reliable than illuminated stylets, retrograde techniques have not gained popularity. With the patient's head flat on the bed and extended, the cricothyroid groove is identified. The skin is prepared with 70% isopropyl alcohol and lidocaine is infiltrated subcutaneously over the cricothyroid groove. Then the procedures illustrated in Fig. 7 are performed. Once the fiberscope is located in the trachea, the wire is removed. The fiberscope is advanced to the carina and the endotracheal tube is passed into the trachea (9).

Flexible Fiberoptic Laryngoscopes. Flexible fiberoptic laryngoscopes have a long and enviable history of use with difficult intubations. They can be used with awake spontaneously breathing patients, anesthetized spontaneously breathing patients, or anesthetized patients receiving controlled ventilation. Numerous intubation aids have been developed over the years. A standard nasal airway can be equipped with an endotracheal tube adapter and inserted into one nostril while the fiberscope is placed in the contralateral nostril or mouth. Oxygen and anesthetic gases can be delivered with spontaneous or controlled ventilation utilizing this system. Similarly, a Guedel-type oral airway can be fitted with an endotracheal tube adapter and placed into the mouth. The fiberscope can then be inserted into either nostril. With this system, oxygen and anesthetic gases can be supplied for spontaneous or controlled ventilation.

Several types of specially manufactured oral intubating airways are available to assist with



Fig. 3. Siker mirrored blade.

oral fiberoptic intubation. They are designed to facilitate passage of the fiberscope through the mouth and into the pharynx. Some provide a distal phalange intended to prevent the tongue from falling posteriorly and blocking the airway (10). In cases where the tongue does fall far enough posteriorly to obscure the view, I have not found the oral intubating airways to be helpful. Additionally, unless the airway is directly in the midline, it tends to maneuver the fiberscope laterally, thereby disorienting the laryngoscopist. I use a standard O-ring bite block to prevent biting on the fiberoptic bundles and dispense with oral intubating airways. Whenever it is necessary to elevate the base of the tongue off the posterior pharynx, I employ jaw thrust or tongue pull.

Alternatives. Continued instrumentation of the airway eventually results in edema. Pharyn-

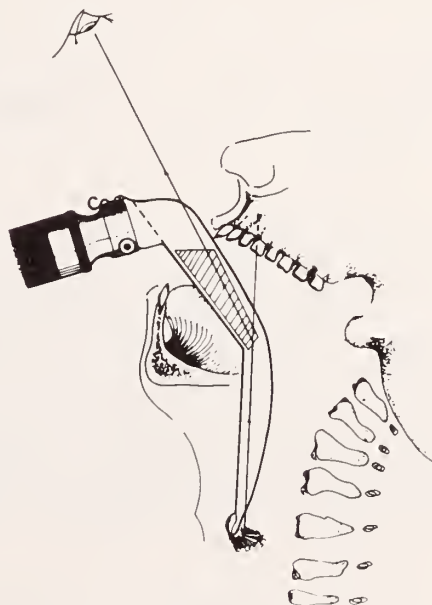


Fig. 4. Bellhouse angulated straight blade. Reprinted with permission from ref. 5.



Fig. 5. Top Bullard laryngoscope.
Fig. 6. Bottom Illuminating stylet.

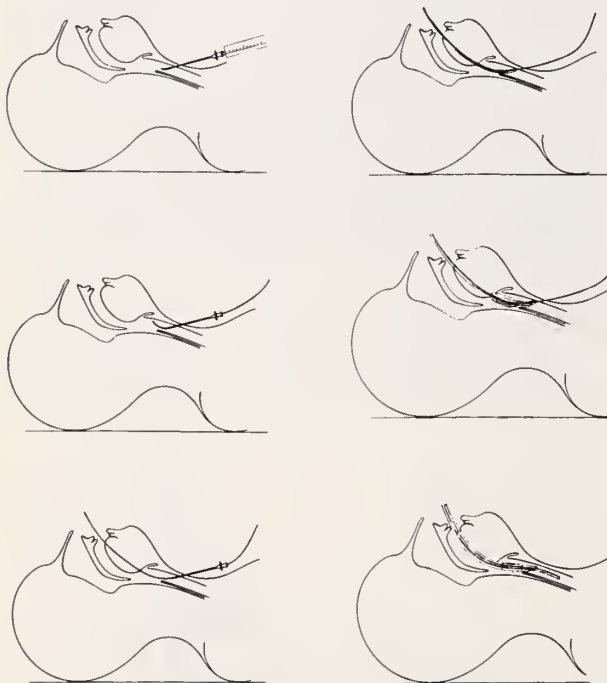


Fig. 7. Retrograde intubation. Catheter and needle are inserted percutaneously through groove and into trachea. Needle is removed, leaving catheter in situ. Correct position is confirmed by aspirating air through catheter with a syringe. Syringe is removed and wire is passed through catheter and is allowed to exit airway through mouth or nose. A flexible fiberoptic laryngoscope, mounted with an endotracheal tube, is passed over wire into larynx and trachea under direct vision. Once fiberscope is located in trachea, wire is removed. Fiberscope is advanced to carina and endotracheal tube is passed into trachea. *Reprinted with permission from Latto IP, Rosen M. Difficulties in tracheal intubation. Philadelphia: Bailliere, Tindall, 1985:99-141.*

geal and laryngeal swelling can convert an easy mask airway into a difficult one and a difficult mask airway into an impossible one. At some point it behooves the anesthesiologist to recognize the potential risk of ventilatory impairment and seek other methods.

If the patient has a good mask airway, it may be advisable to continue anesthesia by mask. For some operations, regional anesthesia may be appropriate, and the patient can be awakened and allowed to breath spontaneously during one of many different types of nerve blocks. Whenever endotracheal intubation is required, the patient can be allowed to emerge from anesthesia and undergo spontaneously breathing flexible fiberoptic intubation. For elective surgery, I prefer to allow edema to resolve over several days and then bring the patient back for proper preparation and awake intubation. In the case of urgent surgery, awake intubation can proceed after proper preparation requiring several hours. Emergent cases require immediate attempts at flexible fiberoptic intubation, tracheostomy, or cricothyroidotomy.

Additional options, such as laryngeal mask airway and esophageal-tracheal combitube, are available.

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Predictable Problems with Flexible Fiberoptic Laryngoscopy

ALLAN P. REED, M.D.

IN CONTRAST TO LARYNGOSCOPY utilizing traditional retraction blades, flexible fiberoptic laryngoscopy is characterized by a limited field of view and requires a special fund of knowledge as well as special skills which facilitate each attempted intubation. The ability to recognize predictable problems and methods of solving them separates the master from the novice. This discussion summarizes many of the predictable problems that occur during flexible fiberoptic intubation (FFI) and describes techniques for solving them.

Need for Formal Instruction. The first documented FFI was performed in 1967 using a choledochoscope (1). During the 1970s, FFI was established as a reliable technique for difficult intubations, but was rarely used (2-6). In the 1980s this technique achieved popularity (7-9). By the 1990s fiberscopes had been redesigned and refined with better optics and other desirable features. Relatively few anesthesiologists are skillful in use of fiberscopes, and the lack of a large cadre of competent teachers has stymied the growth of this technique. The multitude of seemingly minor considerations that contribute to successful fiberoptic intubation are difficult to master without instruction and supervision. Until 1990, there was no outstanding monograph on the subject. At present, few residency training programs offer dedicated periods of time for teaching the technique. Postgraduate instruction is limited to scattered courses across the country, most offering excellent didactics but not conveying the

art along with the science of FFI. Self-instruction seems to be associated with a high failure rate, resulting in abandonment of the technique whenever future opportunities exist for its use (10). Insufficient training is probably the single most common reason for failed FFI (10). Learning appears to be greatest within the framework of formal instruction where attention to details of preparation and hands-on methods are emphasized.

Poor Sensory Blockade Of Airway

Awake spontaneously breathing FFI is indicated for those patients thought to be at increased risk during laryngoscopy. Introduction of foreign bodies into the airway may result in coughing, vomiting, withdrawal, laryngospasm, and tachypnea. Of these reactions, tachypnea is least recognized as a detriment to awake FFI. During inspiration, the larynx moves to its most posterior position, which aids visualization and instrumentation of the structure. Slow, deep inspirations move the larynx posteriorly and maintain it in this position for the longest period. Tachypnea allows the larynx to bob up and down rapidly, thereby impairing visualization and intubation. Any one of these reactions is capable of preventing successful intubation. Abolition of such responses requires afferent sensory interruption, which is critical to the intubation process.

The most frequently encountered problem related to inadequate sensory blockade is improper preparation of the patient. Afferent interruption is predicated on correct use of topical local anesthetics. For topical local anesthetics to work, they must actually contact the mucosa. An intervening layer of secretions acts as a physical barrier, preventing local anesthetics from reaching the mucosa. Consequently, any desiccation of the air-

Presented at the American Society of Anesthesiology Workshop on Fiberoptic Intubation, Boston, Massachusetts, June 26-27, 1993. From the Department of Anesthesiology, Mount Sinai School of Medicine (CUNY), New York, NY. Address reprint requests to the author, Associate Professor of Anesthesiology, Mount Sinai School of Medicine (CUNY), Box 1010, One Gustave L. Levy Place, New York, NY 10029-6574.

way becomes vitally important. Antisialagogues should be administered as premedicants, approximately 1½–2 hr prior to use of topical local anesthetics. This seemingly long period is required to prevent liberation of further secretions and allow previously formed secretions to drain away (10).

Sometimes, small patches of mucosa remain unanesthetized after administration of topical local anesthetics. In such cases additional doses of local anesthetic may be given under direct visualization. Simply identify the area in question and position the fibroscope adjacent to that portion of the airway. Introduce 2 mL of 4% lidocaine through the fibroscope's working channel and wait a few minutes for its onset of action (11). In the unusual circumstance in which this technique of "topping off" the anesthetic is insufficient and when the unanesthetized area exists just above the larynx, superior laryngeal nerve blocks generally solve the problem (12). Laryngospasm is usually amenable to direct vision application of local anesthetics through the fibroscope also. For the rare instance where this maneuver is unsuccessful, transtracheal blocks can solve the problem.

Blood and Secretions in Airway

The view through the fibroscope is limited compared to the panoramic view obtained with traditional retraction blades, and blood and secretions in the airway further restrict the already limited optical field. Prior administration of antisialagogues helps to eliminate secretions and diminishes their importance as an impediment to FFI.

A common mistake is to assume that blood and secretions can be readily and effectively aspirated through the fibroscope's working channel (suction channel). Many practitioners equate the fiberoptic laryngoscope's working channel with that of the bronchoscope and gastroscope. Bronchoscopes and gastroscopes are equipped with larger-diameter insertion tubes containing larger-diameter working channels. The larger working channels on these devices function well to suction blood and secretions. Unfortunately, the smaller working channel of fiberoptic laryngoscopes functions as an inefficient suction apparatus. The negative pressure achieved at the scope's end is attenuated to the point where application of suction serves to draw blood and secretions toward the objective lens without eliminating them from the airway. Consequently, application of negative pressure to the fiberoptic

laryngoscope's working channel often further impairs an already poor view. Blood and secretions are best aspirated through standard large-bore suction catheters or tonsil tip suction devices. These devices can be introduced, by an assistant, through the mouth or nose and directed to the pooled blood and secretions (11).

Although application of negative pressure to the working channel tends to be counterproductive, the channel can potentially serve a useful purpose. Flowing oxygen through the channel pushes blood and secretions away from the objective lens, thereby preventing further obstruction of the view.

Once blood or secretions contact the objective lens, vision through it becomes blurred. Persistent contact of the lens with these substances requires removing the fibroscope from the patient and cleaning the instrument with a gauze or alcohol pad (10).

Fogging of Objective Lens

Fiberscopes are stored at room temperature. The patient's airway is warm and humid. Consequently, introduction of the scope into the patient results in condensation forming on the objective lens. Attempts at preventing this problem with warm water baths, pHisoHex dips, and other lens coatings are only marginally successful. Best prevention is achieved with oxygen. Oxygen is supplied as a dry gas. As it flows through the working channel and exits the fibroscope, oxygen blows past the objective lens and evaporates whatever condensation forms on it. Consequently, fogging is prevented.

Whenever fogging of the objective lens does occur, the scope should be removed and the tip wiped clean with a gauze or alcohol pad.

Obstructed Laryngeal View

Obstruction of the laryngeal inlet by a floppy epiglottis occurs occasionally and is a difficult problem. The awake spontaneously breathing patient can be instructed to take slow, deep breaths, which bring the larynx to its most posterior position and improve exposure. In the awake patient or the anesthetized patient, jaw thrust or tongue pull may be helpful. These maneuvers lift the epiglottis anteriorly, thereby moving it out of the line of vision.

Less commonly, the floor of the mouth and base of the tongue may be elevated toward the epiglottis by tumor or edema, resulting in obstructed laryngeal view. In this circumstance, a traditional retraction blade may be inserted into

the airway in an attempt to elevate the base of the tongue out of the line of vision (10).

Abnormal Airway Anatomy

Airway anatomy may be distorted by a deviated nasal septum, previous surgery, tumor, edema, or radiation therapy. In the case of deviated nasal septum, introduction of a fiberscope through the nose tends to direct the scope laterally. Identification of the airway is therefore achieved by rotating the fiberscope medially.

Previous surgery, tumor, edema, and radiation therapy tend to displace the larynx laterally. Nasal approaches are facilitated by selecting the ipsilateral nostril. In other words, select the nostril on the side toward which the larynx is deviated. For oral techniques, the obscured larynx is often located following fiberscope rotation toward the side to which the larynx is deviated. Often, awake spontaneous respirations facilitate identification of the larynx as that structure which moves with respiration.

Depending on the type of airway distortion and relative airway anatomy, it may be possible, in some cases, to direct the fiberscope into the trachea, but not the endotracheal tube. In such cases, trials of different-size tubes, armored tubes, tongue pulls, and jaw thrusts may be of assistance. In some instances, the insertion tube can be gently maneuvered around a partially obstructing tumor, but advancement of the endotracheal tube may risk avulsion and/or bleeding (10).

Inability to Advance The Fiberscope

Generous lubrication of the fiberscope often impairs advancement into the airway, because the laryngoscopist's fingers cannot grip the insertion tube. Better manipulation of the scope is achieved by interposing a dry gauze pad between the operator's fingers and the insertion tube.

Inability to Advance Endotracheal Tube over Fiberscope. Inability to thread the endotracheal tube over the insertion tube is generally due to a relative mismatch between the two. Not all fiberscopes have the same cross-sectional diameter. Therefore, a particular endotracheal tube that threads well over one scope may not do so over another. Generally, the smallest endotracheal tube appropriate for a given scope is 1.5 mm larger than the insertion tube. The absolute smallest usable size of endotracheal tube is a function of insertion tube tolerances, endotracheal tube tolerances, lubrication, and final threading configuration of the insertion tube. Since the

endotracheal tube adapter occupies space within the endotracheal tube, removal of the adapter facilitates manipulation of relatively small endotracheal tubes over any particular insertion tube.

Lubrication facilitates threading of the endotracheal tube over the insertion tube. Water-soluble lubricants tend to desiccate rapidly in the dry air of the operating room. After they dry, a residue remains which increases friction between endotracheal tube and fiberscope. Consequently, if water-soluble lubricants are selected, they should be applied shortly before the fiberscope is actually used. Nonaqueous-based lubricants tend to dry more slowly and allow preparation of the scope well in advance of its actual use.

Utilizing the nasotracheal route, it is sometimes impossible to advance the endotracheal tube over the fiberscope into the pharynx. A bony prominence emanating from the hard palate will occasionally stenose the communication between the nose and pharynx. The opening will remain large enough to allow passage of an insertion tube, but not an endotracheal tube. Either a smaller endotracheal tube must be employed, the contralateral nostril used, or the oral approach attempted.

If an oral endotracheal tube does not pass beyond the base of the tongue, then pull the tongue forward and lubricate the outside of the endotracheal tube to reduce friction between the plastic tube and the dry mucosa.

Often, the endotracheal tube will abut the right arytenoid, preventing passage into the larynx. This obstruction is readily overcome by retracting the endotracheal tube approximately 2 cm, turning it 90 degrees counterclockwise, and advancing it once again. This maneuver brings the pointed tip of the endotracheal tube from the right lateral position to the anterior position. The tube will then slip underneath the epiglottis and into the laryngeal inlet. In the rare instances where counterclockwise rotation does not allow passage of the tube, try other maneuvers designed to align airway anatomy. These include tongue pull, jaw thrust, deep spontaneous inspiration, and lifting base of tongue with a retraction blade.

Inability to Withdraw Fiberscope

After the endotracheal tube is successfully placed, inability to withdraw the fiberscope from the tube occurs occasionally. Inadequate insertion tube lubrication is the most frequent cause of such problems. It may be necessary to withdraw

the scope and endotracheal tube as a single unit. Lubrication can then be augmented and the entire sequence begun again.

Occasionally, the fiberscope's tip may remain flexed. In this position, the endotracheal tube does not fit over the fiberscope. Generally, persistent flexion is caused by inadvertent engagement of the locking mechanism. Simply release the lock, straighten the tip, and remove the scope from the endotracheal tube. Unless the tip can be unlocked and straightened, it is necessary to remove the scope and tube as a single unit, straighten the tip, and begin again.

On rare occasions the endotracheal tube becomes entrapped within the tube's Murphy eye (13, 14). When this occurs, it is almost impossible to extricate the insertion tube. It is necessary to remove the scope and tube as a single unit. The fiberscope can then be freed from the Murphy eye and the process begun again.

Mask and Airway Problems

Specially designed masks with endoscopy ports exist for the placement of fiberscopes during controlled ventilation by face mask (15-17). The endoscopy port contains a rubber diaphragm which deteriorates as the mask ages. Instrumentation of old diaphragms sometimes results in soiling of the airway as it fragments.

Numerous oral airway intubators have been designed (18, 19). One universal problem with these devices is lateral displacement of the fiberscope if the oral airway is seated improperly. Unless the oral intubator is placed directly in the center of the airway, the laryngoscopist can readily become disoriented.

Inflexible Fiberscope Tip

Inability to flex the fiberscope tip is generally due to one of three causes. If the insertion tube does not bend prior to being placed within the lumen of the endotracheal tube, one or two of the angulation wires running down the length of the insertion tube may be broken. This requires repair at the factory and nothing can be done to correct the problem in the hospital. More commonly, the locking mechanism has been inadvertently engaged. Simply move the locking lever to the unlocked position and the tip should respond to displacement of the trigger.

If the tip does not respond after the endotracheal tube and fiberscope are placed into the patient, another problem may exist. Often, the bending portion of the insertion tube remains within the lumen of the endotracheal tube. Con-

sequently, the rigid endotracheal tube encases the insertion tube and prevents deflection of the tip. When this occurs, resistance to moving the deflection trigger is often appreciated. To correct such problems, simply advance the fiberscope or withdraw the endotracheal tube a few centimeters in order to extend the bending portion of the insertion tube beyond the tip of the endotracheal tube.

Visual Field Difficulties

Slight Epistaxis. Even small amounts of blood in the airway can impair vision through the fiberscope. Sometimes it is possible to tamponade the bleeding by placing a nasal airway into the nares from which epistaxis is emanating. To accomplish this, take a nasal airway and slit it longitudinally. Insert the airway into the side experiencing epistaxis. Then pass the fiberscope through either the contralateral nostril or the nasal airway. If the scope is advanced through the nasal airway, it can be removed via the longitudinal slit later.

Pink or White Field. Often, the visual field appears pink or white. No identifiable structures are seen. This usually results from placing the objective lens against airway mucosa. To correct this problem, simply move the fiberscope backward until the vision improves.

Insufficient Light. Fiberoptic laryngoscopes are relatively small compared to bronchoscopes and other endoscopes (20). Consequently, they contain fewer fiberoptic bundles to transmit light. If the visual field appears dim when the scope is first used, confirm that the rheostat on the light source is turned to maximum illumination.

Sometimes, illumination will be sufficiently strong at the beginning of laryngoscopy but will start to dim as time goes on. When this occurs, the light cable may have been partially pulled from its receptacle in the light source. This problem is easily corrected by replacing the light cable into its receptacle.

Dark Spots in Visual Field. Dark spots in the visual field represent broken fiberoptic bundles. They cannot be repaired or replaced in the hospital. Correction of this problem requires return of the instrument to the factory. A small number of spots or those located in the periphery are generally inconsequential. Significant numbers of spots or those located centrally may render the scope unusable.

Blurred Image. Visual acuity differs considerably from one individual to another. Consequently, each user must focus the fiberscope for

his or her own eyes. This is accomplished by pointing the objective lens at some printed material and manipulating the focusing ring until the image becomes sharply defined. Failure to focus the scope prior to its use frequently results in blurred vision.

Impaired acuity may also result from fogging of the lens, which is preventable by passing oxygen through the working channel. A coating of lubricant, blood, or secretions covering the lens will also cause poor vision. To correct this problem, simply wipe the lens clean.

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Flexible Fiberoptic Bronchoscopy:

A Practical Guide to Examining Infants and Children

I. DAVID TODRES, M.D., AND NATAN NOVISKI, M.D

FLEXIBLE FIBEROPTIC BRONCHOSCOPY for infants and children was a natural development following introduction of flexible fiberoptic bronchoscopy for adults. The procedure has added to the diagnostic and therapeutic armamentarium of pediatric pulmonologists, intensivists, anesthesiologists, and otolaryngologists (1-5).

Differences between Rigid and Flexible Bronchoscopes

Differences between rigid and flexible fiberoptic bronchoscopy must be appreciated in order to individualize specific techniques for appropriate clinical conditions. The size, flexibility, auxiliary instrumentation, optics, and type of sedation used in each procedure differ. The flexible bronchoscope is sized according to outer diameter (e.g., 3.5 mm), and the patient breathes around the instrument. The rigid bronchoscope is sized according to its internal diameter; thus, a 3.5-mm rigid bronchoscope has a 4-4.5-mm outer diameter and the patient breathes through the instrument.

Rigid bronchoscopes permit passage of instruments such as suction catheters as well as forceps for biopsies and extraction of foreign bodies through the lumen. In flexible bronchoscopes for children, the limited internal diameter (1.2 mm) of the suction channel restricts use to few instruments. The glass rod fiberoptic telescope used in the rigid bronchoscope provides excellent optical characteristics. Optics in the flexible bron-

choscope are also excellent and offer the advantage of maneuverability, allowing visualization of areas the rigid bronchoscope may not reach. The flexible bronchoscope also makes it possible to study airway dynamics because most examinations can be performed with the patient under mild sedation and local anesthesia. Rigid bronchoscopy necessitates deep general anesthesia, which obscures dynamic airway resistance alterations. Flexible fiberoptic bronchoscopy has become an especially valuable tool for performing tracheal intubation in patients for whom conventional laryngoscopy is unsuccessful or anticipated to be associated with harmful effects. One classic example is the patient with cervical neck injury.

Indications

Bronchoscopy of adults is largely concerned with malignancy. Bronchoscopy of younger patients centers on airway obstruction, infection, congenital anomalies, and foreign bodies. One needs to determine when a patient may benefit from bronchoscopy by assessing the risk-benefit ratio of the procedure and recognizing the limitations of the flexible bronchoscope. At times, bronchoscopy will not reveal significant pathology. Normal airway findings can be reassuring to parents as evidence ruling out an underlying ominous condition.

In the majority of cases, bronchoscopy is performed for diagnostic purposes. Major indications for use of the flexible and the rigid instrument differ (Table). Therapeutic applications are generally limited to treatment of airway obstruction from foreign bodies, mucus plugs, mucoid impactions, granulation tissue, or tumors. The bronchoscope is individualized to each case. Possible treatments include bronchoalveolar toilet and laser resection.

From the Department of Anaesthesia (IDT) and Paediatrics (NN), Harvard Medical School, and the Neonatal and Pediatric Intensive Care Units, Massachusetts General Hospital, Boston (NN, IDT). Address reprint requests to Dr. I. David Todres, Director, Neonatal and Pediatric Intensive Care Units, Massachusetts General Hospital, Boston, MA.

The most common indication for bronchoscopy in the younger patient is stridor. Examination of the patient is best carried out when symptoms are most prominent. The initial symptom of laryngeal and supralaryngeal abnormalities is usually inspiratory stridor. However, 14% of laryngeal or supralaryngeal abnormalities with stridor are associated with additional abnormality below the glottis. Therefore, a complete bronchoscopy is recommended in every patient with stridor. Limited procedures may be considered for abnormalities causing severe narrowing of the airway, such as subglottic stenosis or edema.

The major diagnostic findings during upper airway bronchoscopy for stridor include laryngomalacia, subglottic stenosis, and vocal cord paralysis. When the primary symptom is persistent expiratory wheezing, tracheal or bronchial malacia, foreign body aspiration, and tracheal compression are the most common causes. Other common findings during flexible bronchoscopy include inflammatory changes, granulation tissue, mucus plugs, and anatomic variants. The major findings following rigid bronchoscopy are foreign body, laryngomalacia, tracheomalacia, and mucus plugs.

Laryngomalacia is the most common laryngeal problem in infancy. Endoscopic findings reveal a soft, elongated, omega-shaped epiglottis or large arytenoids, which prolapse into the glottis during inspiration, or short aryepiglottic folds with a relatively large epiglottis. An important benefit of flexible bronchoscopy is that it allows examination of upper airways with the head in the natural position. In cases where stridor is due

to nasopharyngeal abnormalities, such as large adenoids or collapse of the pharyngeal walls, flexible bronchoscopy provides visualization of these structures via the nasal approach.

The subglottic region should be carefully examined in a stridorous patient where laryngeal causes are not found, to explain the "noisy breathing." Sometimes in an apparently normal subglottic region, the 3.5-mm flexible bronchoscope may pass with difficulty through the cricoid ring, impeding the small infant's ability to breathe around it. The subglottic region can be stenotic due to congenital malformations or to acquired lesions. The bronchoscopist can evaluate the degree of obstruction, information crucial to future endotracheal intubation. Examination of the vocal cords includes their baseline (resting) position and their dynamic (phonating or crying) position. Normal vocal cords open during inspiration and close during expiration. Hemangiomas in the airways are often associated with hemangiomas on the body surface. When a child with suspected hemangioma is well sedated, the tumor may be less prominent and the epithelium covering the hemangioma may mask its vascularity. The endoscopist should be familiar with this potential problem and look for loose, wrinkled mucosa. The child should be stimulated to cry or strain to "bring out" the hemangioma. The normal trachea consists of cartilage rings, the posterior portion of which is membranous. In tracheomalacia, the tracheal walls collapse during expiration and the posterior and anterior walls may come into contact, leading to severe airway obstruction. Tracheomalacia may be caused by external compression of the airways, such as a vascular ring or enlargement of the heart and great vessels.

A foreign body should always be suspected in a child with persistent or recurring pneumonia or atelectasis. We recommend rigid bronchoscopy for all cases of suspected foreign body aspiration. Even when the index of suspicion for foreign body is not high, it is advisable to perform flexible bronchoscopy in the operating room so that in the event a foreign body is located, it can be removed with rigid bronchoscopy performed under general anesthesia (6). When a child has hemoptysis, we recommend rigid bronchoscopy. Bronchoscopy may assist in the investigation of pulmonary infiltrates (recurrent or persistent) through bronchoalveolar lavage (7, 8). The fluid should be examined for lipid-laden alveolar macrophages to rule out aspiration syndromes (9). Apart from diagnostic applications of flexible bronchoscopy noted above, its great value for the anesthesiologist lies in facilitation of tracheal intubation

TABLE
Major Indications for Use of Flexible and Rigid Bronchoscope

Flexible	Rigid
Persistent stridor, cough, hoarseness, wheezing, atelectasis	Foreign body removal
Sleep-associated airway obstruction	Hemoptysis
Recurrent or persistent pneumonia	Substitute for flexible bronchoscopy because pt is ● uncooperative ● neonate or young infant on mechanical ventilation in whom flexible bronchoscope cannot pass through endotracheal tube without compromising oxygenation and ventilation
Lavage for diagnosis or therapy	
Evaluation of tracheostomy	
Performance of difficult intubation	

when conventional laryngoscopy is unsuccessful or its implementation may be associated with injury. A typical example would be a patient who has a cervical cord injury.

Equipment

The standard pediatric flexible fiberoptic bronchoscope is about 3.5 mm in outer diameter. It consists of a flexible shaft through which passes a 1.2-mm suction channel and two glass fiber bundles. One bundle brings light to the tip of the bronchoscope and one bundle carries the image. The distal 2.0–2.5 cm of the instrument is movable and can be flexed approximately 160 degrees in one direction and 60 degrees in the opposite direction. The suction channel is used to aspirate, irrigate, provide supplemental oxygen, perform bronchial lavage, and pass instruments. Cytology brushes, small grasping forceps, and baskets are designed to fit through the suction channel. Smaller-diameter bronchoscopes (1.8 mm, 2.2 mm, and 2.7 mm) are also available. Most of them offer limited manipulation of the tip and do not provide a suction channel. The equipment must be adequately cleaned and sterilized after each bronchoscopy procedure.

Procedure

Flexible bronchoscopy should be performed in a location where instruments, monitors, and medications necessary for the patient's safety are available. Skilled assistants are important. Assistants prepare and stabilize patients prior to bronchoscopy; monitor heart rate, ventilation, and oxygenation (SpO_2); aid the bronchoscopist during the procedure; and provide postbronchoscopy care.

Generally, patients should be sedated (10). The first step in the sedation process begins with appropriate psychological preparation. An explanation of upcoming events, delivered in a positive and relaxed fashion, will often result in the child's cooperation. Newborns or other patients who have severe respiratory compromise and are at risk for respiratory depression should receive minimal sedation. In selected cases, only topical anesthesia should be used. Patients should be given nothing per mouth for four hours and should have an intravenous catheter in place. Sedatives are preferably administered intravenously. The ideal agent still eludes us. However, a number of single agents or agents in combination work satisfactorily: intravenous meperidine only, chloral hydrate and intravenous meperidine, or midazolam and morphine. Topical anes-

thesia is required, employing lidocaine without preservatives to a total dose of 5 mg/kg. It has an anticipated duration of action of approximately 20–30 min. Lidocaine is instilled into the nose before instrumentation and through the suction channel as bronchoscopy proceeds. Good laryngeal anesthesia is essential. Because topical lidocaine's onset of action is 2–3 min, one should wait this period of time after lidocaine irrigation before proceeding with further advancement of the instrument. Topical anesthesia is recommended even if patients are intubated and sedated or are receiving general anesthesia. Lidocaine may be absorbed into the systemic circulation, with possible toxic effects. Thus its use should be limited to recommended safe dosages (11).

The flexible bronchoscope is generally inserted through the nose. This route allows for an easier, more stable, and safer passage. It provides important information regarding the patient's nasopharyngeal passages and improved visualization of the larynx (Fig.). The 3.5-mm standard pediatric flexible bronchoscope slides through the nasal passages of most children, even neonates. During the procedure, supplemental oxygen is administered through a nebulization mask containing a central hole, through which the bronchoscope can be inserted into the nose. In intubated children, the flexible bronchoscope can be passed through the endotracheal tube to verify the position of the tube, to explore the airway, and to provide suction and clearing of specific air passages.

Use of the flexible bronchoscope to facilitate tracheal intubation is especially important in the operating room, emergency room, and intensive care unit. The 3.5-mm bronchoscope may be used to insert a 4.5-mm inner-diameter (I.D.) endotracheal tube. The 2.2-mm bronchoscope can be used with a 3.0-mm I.D. tube and even a 2.5-mm I.D. endotracheal tube. We recommend passing the tip of the flexible bronchoscope through the endotracheal tube (lubrication of the bronchoscope is required), inserting the tip of the bronchoscope through the nose, larynx, and trachea, and only then threading the endotracheal tube through the larynx to the trachea. At the laryngeal inlet, counterclockwise rotation (90 degrees) will facilitate passage of the tube through the glottic opening. The bronchoscope can be used, subsequently, to verify position of the endotracheal tube. Using an endotracheal tube larger than 6.0 mm I.D. may cause damage to the standard pediatric flexible bronchoscope. This also applies to the ultrathin bronchoscope with a tube larger than 4.5

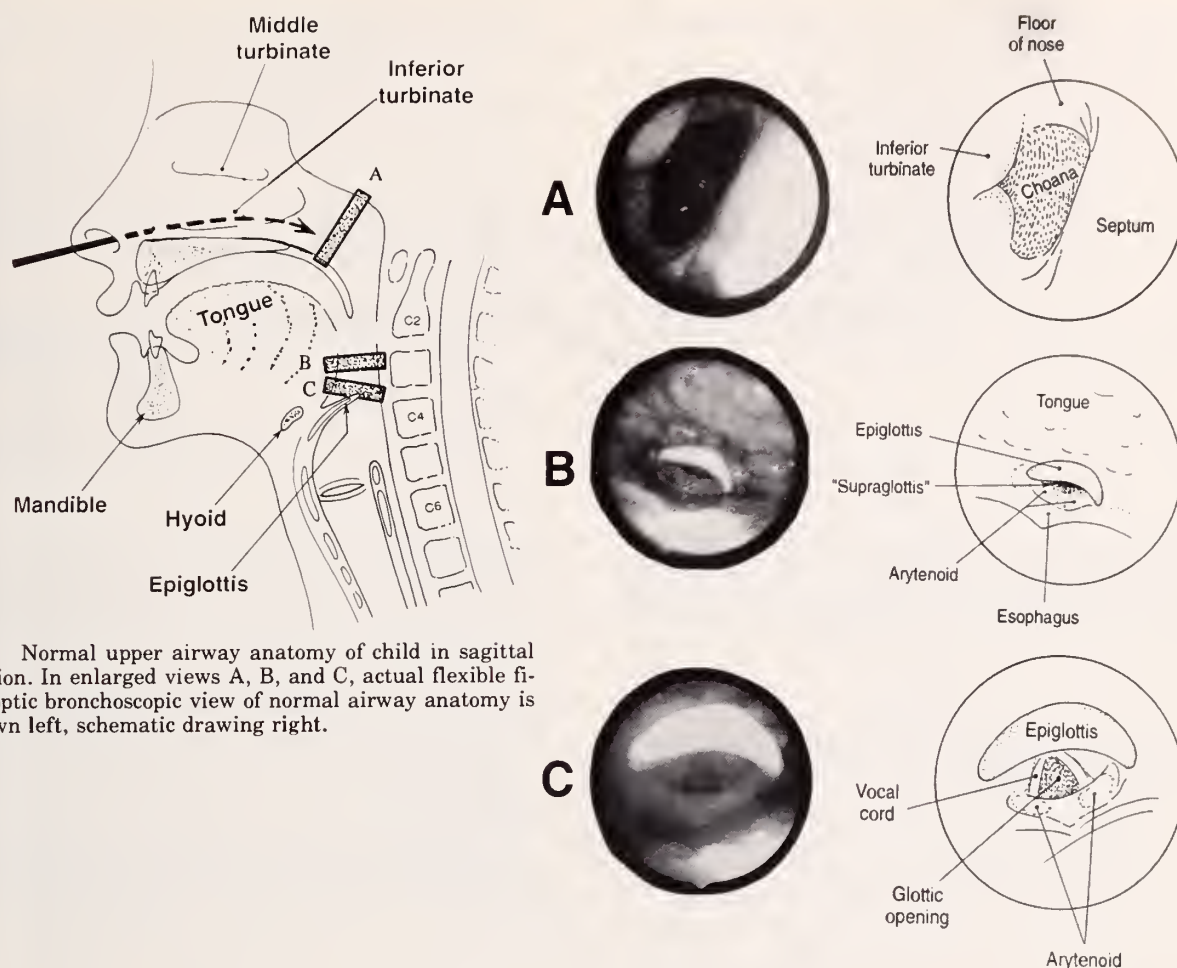


Fig. Normal upper airway anatomy of child in sagittal section. In enlarged views A, B, and C, actual flexible fiberoptic bronchoscopic view of normal airway anatomy is shown left, schematic drawing right.

mm I.D. Flexible bronchoscopy is also used for evaluating tracheostomy stomas and tubes. This may be carried out via the stoma, tube, or larynx.

Bronchoalveolar lavage may be performed with the flexible bronchoscope. The lavage fluid for diagnostic purposes is examined for organisms and cytology. Special staining for fat is required to rule out aspiration syndromes. Stains for hemosiderin, *Pneumocystis carinii*, and others may also be performed. Therapeutic use of lavage is mainly to clear the airways of thick secretions.

Complications and Contraindications

Relative contraindications to flexible bronchoscopy include bleeding disorders, massive hemoptysis, severe airway obstruction, critical illness, and preexisting hypoxemia. Clinical judgment and appropriate assessment of each individual situation are essential when considering a patient for flexible bronchoscopy. Recognized complications include hypoxemia, hypercapnia with acidosis, arrhythmias, laryngospasm, bronchospasm, infection, pneumothorax, hemoptysis, di-

rect trauma to the nasal passages or larynx, and subglottic edema with stridor. In addition, adverse reactions to medications administered during the procedure add to the complications that may be associated with flexible bronchoscopy.

Hypoxemia is of primary concern. Its incidence may be reduced by providing supplemental oxygen via a special mask and close respiratory monitoring. Hypercapnia is more difficult to monitor. Attention to chest movement and air entry as well as expeditious performance of bronchoscopy helps to limit hypercapnia and acidosis.

Arrhythmias may be due to hypoxemia or vagal stimulation. Bradycardia during the procedure is treated by withdrawing the bronchoscope and ensuring adequate oxygenation. Hypoxemia is prevented by ensuring adequate oxygenation, and vagal stimulation is limited by profound anesthesia of the larynx. Some bronchoscopists routinely administer atropine before or during bronchoscopy to prevent bradycardia.

Postbronchoscopy, mild stridor due to subglottic or laryngeal edema may be heard. In most cases, it does not prolong the child's hospitalization. Racemic epinephrine inhalations may be ad-

ministered in severe cases to alleviate the obstruction.

Pneumothorax is a rare complication of bronchoscopy. One report cites two cases out of 1,095 flexible bronchoscopies (1). Direct trauma to the nasal passages and the larynx should be prevented, but occasionally epistaxis or hemoptysis occurs. Generally the bleeding stops spontaneously. A report comparing complications of rigid and flexible bronchoscopies in adults has shown a lower complication rate associated with flexible bronchoscopies (12).

We do not withhold bronchoscopy in any case where we are convinced that the child needs the procedure. One should be especially careful in children with bleeding disorders, critical illness, and hypoxemia. In these cases, we recommend performing rigid bronchoscopy in the operating room under controlled conditions with surgical and anesthesiology teams present.

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Learning Fiberoptic-Guided Endotracheal Intubation

JAMES N. KOPPEL, M.D.

THE FIBERSCOPE is by no means an experimental instrument. It has been in clinical use since 1967 and is a legitimate, state-of-the-art tool for both airway evaluation and management. Pulmonologists, otolaryngologists, gastroenterologists, thoracic surgeons, and anesthesiologists routinely employ fiberoptic devices in the course of their practices. The goal of all postgraduate flexible fiberoptic airway workshops is to enable the practitioner to successfully introduce the instrument into his or her practice of anesthesiology and airway management. Fiberoptic-guided intubation is a technical skill, mastery of which is predicated on motivation. With practice, manipulation and positioning of the flexible fiberscope can become as natural an act as using conventional rigid laryngoscope blades. Flexible fiberoptic-guided intubation should be considered along with other procedural skills performed by anesthesiologists on a daily basis, such as placement of central venous catheters or continuous epidural catheters. No anesthesiology resident can be considered to have successfully completed training unless proficiency with fiberoptic instruments is achieved.

Commonly, the neophyte endoscopist attempts use of the fiberscope for the first time to intubate a difficult airway. Sometimes, the fiberscope is used following multiple unsuccessful direct laryngoscopies. Secretions, edema, and blood associated with trauma to airway mucosa often prevent distinct visualization of anatomic struc-

tures. Overwhelming frustration is likely to ensue, and failure to intubate is almost a certainty. Unfortunately, abortive experiences with the fiberscope in these situations foster contempt for the instrument. As a result, the disillusioned anesthesiologist is least likely to select this technique in the future when faced with an airway that is anticipated to be complex from the start.

Is Learning on Patients Safe?

Flexible fiberoptic-guided endotracheal intubation is a benign procedure. The incidence of sore throat following conventional rigid laryngoscopy and endotracheal intubation is similar to that after fiberoptic-assisted intubation (1). There is no evidence that use of fiberoptic techniques for normal airways causes an increased incidence of oropharyngeal trauma or other related problems. Patients at increased risk for aspiration pneumonia are not ideal teaching cases. This group includes the massively obese, diabetics with evidence of autonomic dysfunction including gastroparesis, and those with a history of symptomatic esophageal reflux.

During and after flexible fiberoptic-guided endotracheal intubation, hemodynamic parameters, including heart rate and blood pressure, remain relatively stable. A comparison of nasotracheal intubation using the fiberscope and the Macintosh blade revealed a clinically insignificant increase in heart rate (2).

Another study comparing oral fiberoptic intubation and conventional rigid laryngoscopic intubation during intravenous propofol anesthesia demonstrated no significant differences in hemodynamic profiles between the two intubation modalities (1).

When fiberoptic-guided intubation techniques are selected, it is critical to provide ade-

Presented at the American Society of Anesthesiologists Workshop on Fiberoptic Intubation, Boston, Massachusetts, June 26-27, 1993. From the Department of Anesthesiology, The Mount Sinai Medical Center, New York, NY. Address reprint requests to James N. Koppel, M.D., Clinical Director, Department of Anesthesiology, Long Island Jewish Medical Center, New Hyde Park, NY 11042.

quate levels of anesthesia. Sufficient depth of general anesthesia is required to prevent awareness and ensure hemodynamic stability. When fiberoptic intubation is performed with the patient sedated or fully awake, profound airway anesthesia is necessary to ensure patient comfort, cooperation, and hemodynamic stability.

How Long Will Learning Take?

Whereas pulmonologists must learn the mechanics of flexible fiberoptic bronchoscopy in the relatively few patients requiring a thorough evaluation of their airways, anesthesiologists have the opportunity to learn its use on most patients scheduled for surgery who require general endotracheal anesthesia. Therefore, the amount of clinical material available to the anesthesiologist is vast, and motivated individuals can gain experience quickly. An intense, concentrated effort expended on learning the technique yields gratifying results.

A follow-up survey of formalized instruction including lectures and manikin practice sessions demonstrated an increased frequency of fiberoptic use and improved success rates in subsequent independent practice (3).

Johnson and Roberts studied four anesthesiology residents who initially practiced with the fiberscope on manikins under the guidance of an instructor. They then employed the fiberscope to intubate patients after the induction of general anesthesia, including muscle relaxants. It was concluded that an acceptable level of proficiency can be achieved after 10 oral fiberoptic-guided intubations (4). Following the tenth patient, intubation times remained constant at between 1.2 and 1.5 min. Delaney and Hessler performed 60 consecutive nasal intubations themselves in the emergency room using the flexible fiberscope and topical anesthesia wherever possible (5). The personal experience of these highly motivated physicians demonstrated that 10 cases were required to gain sufficient proficiency to allow fiberoptic-guided endotracheal intubation to occur in a timely manner. After intubation of 10 patients, the average time to completion of a nasal fiberoptic-guided intubation was $3 (\pm 2.4)$ min.

Why Use Models?

Historically, models have been used to teach a host of medical procedures, including conventional rigid laryngoscopy and endotracheal intubation, cardiopulmonary resuscitation, and nerve blocks. Models facilitate the acquisition of skills required for successful use of the flexible fiberscope. They allow the learner to familiarize him-

self or herself with the capabilities and limitations of the instrument and facilitate earlier development of psychomotor skills necessary to successfully direct the instrument with precision.

It is recommended that the novice practice maneuvering the flexible fiberscope while watching the progress of the instrument's tip under direct external vision. Working with models helps the trainee learn proper manipulation of the scope, which will eventually facilitate guidance in the desired direction. It is necessary to master the technique of rotating the control head to change tip orientation and to appreciate its limitations of anterior and posterior motion. Then, after some degree of facility is acquired, the learner should employ the system's optics while completing similar maneuvers using manikins. The field of view at varying distances from the tip of the instrument can also be recognized. Anatomically correct models are useful for learning the approximate distances and relationships between critical upper airway landmarks. It is important to keep the fiberscope in as straight a line as possible, without bends or curves. This concept is readily reinforced during sessions with various manikins.

Commercial models exist in several varieties, including a human intubation manikin, a rubberized cast of the tracheobronchial tree, and a nonanatomic model aptly named "hit-the-hole." All are designed to challenge the learner and allow continual improvement of psychomotor performance.

- **Hit-the-Hole** (nonanatomic lucite): Cedric R. Bainton, M.D., Anesthesia Research Foundation, Department of Anesthesia, Rm 3S-50, San Francisco General Hospital, 1001 Potrero Avenue, San Francisco, CA 94110; phone (415) 206-3245
- **Tracheobronchial model** (anatomic latex): Richard Wolf Medical Instruments Corporation, 353 Corporate Woods Parkway, Vernon Hills, IL 60061; phone (800) 323-WOLF; (708) 913-1113; (708) 913-1488 FAX

Making Your Own Model. Simple models can easily be created from rolls of adhesive tape and paper clips. Bumpers and blockers placed creatively in pinball machine fashion can manufacture unique challenges to advancement of the fiberscope while viewing through its optical system. Alternatively, small pencil-sized holes can be punched at different levels in opposing sides of a small cardboard box. The scope can be inserted through one hole, and the instrument

maneuvered and directed through the second hole while employing the optical system.

Any variety of model, either commercial or homemade, anatomic or nonanatomic, will prove useful in learning proper handling of the fiberoptic, if sufficient time is spent practicing on the device.

Intubation Aids and Accessories

Various airways have been developed to aid the novice when using the fiberoptic scope. These devices are designed to retract the tongue anteriorly, away from the palate and posterior pharyngeal wall. This may be critical in the anesthetized, paralyzed patient, where collapse of soft tissues may be more extensive than in the awake, spontaneously breathing subject. The objective is to increase the pharyngeal space and maintain the fiberoptic in the midline position. However, the oral airway may fail to ideally position either the tongue or the epiglottis. A malpositioned oral airway may enter the piriform fossa. In these instances, the fiberoptic can be directed into a blind pouch rather than toward the laryngeal opening.

Several oral intubating airways exist. The Ovassapian intubating airway, Williams airway, and Patil-Syracuse airway are three popular examples.

The Ovassapian intubating airway prevents an awake patient from biting on the fiberoptic and damaging the delicate fiberoptic bundles. A widened distal end is designed to retract the tongue, and a semiclosed channel comprising the posterior surface guides the fiberoptic and also allows easy removal from the endotracheal tube when successfully passed into the trachea (from Kendall Healthcare Products Company, 15 Hampshire Street, Mansfield, MA 02048; phone (800) 962-9888).

The Williams airway is a clear plastic oropharyngeal airway that is cylindrical on the proximal half and opens at the distal half onto the lingual surface. It permits simultaneous insertion of the fiberoptic and endotracheal tube and is easily removed after intubation. Another variation, the reusable metal Patil-Syracuse airway, serves a similar function.

The Patil-Syracuse endoscopic mask allows oxygenation, positive pressure ventilation, and concurrent administration of general anesthesia. Thus, fiberoptic-guided endotracheal intubation can proceed during general anesthesia with a reduced risk of hypoxemia and hypercarbia. The endotracheal tube and fiberoptic are inserted through the mask's diaphragm and directed into

the oral pharynx. Using this technique, the learner can spend virtually an unlimited amount of time exploring the pharynx, visualizing the vocal cords, and passing the fiberoptic. An assistant may ventilate the anesthetized patient or the patient may be allowed to breathe spontaneously. However, deterioration of the diaphragm has been reported, which creates a potential hazard if carried into the airway.

Should These Aids Be Used? I believe these devices are unnecessary in the early stages of learning and after proficiency has been achieved. Unquestionably, successful fiberoptic-guided endotracheal intubation can be accomplished without accessories, even by the neophyte endoscopist. Additionally, these aids may be unavailable at the moment when an urgent fiberoptic-guided intubation is required. For this reason, reliance on guides and airways can be a hindrance rather than a help, and I encourage training in fiberoptic-guided endotracheal intubation without reliance on these devices.

How Anesthesiology Residents Are Taught at The Mount Sinai Medical Center

As of this writing, anesthesiology residents at The Mount Sinai Medical Center in New York participate in a two-week intensive instructional block in which fiberoptic-guided endotracheal intubation is taught by an experienced instructor. During this training period, each resident is assigned to an attending anesthesiologist for contact with specific patients. ASA class I and II patients who presumably possess normal airway anatomy and require general endotracheal anesthesia are selected for teaching purposes. Patient exclusion criteria include significant disease of any major organ system and increased risk of aspiration pneumonitis.

Obese patients are poor candidates because they desaturate rapidly, are predisposed to aspiration pneumonitis, and are technically more difficult to fiberoptic due to extensive oropharyngeal soft tissue collapse after induction of anesthesia and onset of muscle relaxation.

All patients receive preoxygenation (denitrogenation) by anesthesia face mask with 100% oxygen (Table 1). After induction of general anesthesia with large doses of propofol or thiobarbiturate, the patient's eyes are taped shut to reduce the potential for ocular injury. Ability to ventilate by mask is confirmed, and a rapid-onset, short-duration, nondepolarizing neuromuscular blocker such as vecuronium or mivacurium

TABLE 1

Recommendations for Learning Fiberoptic-Guided Intubation under General Anesthesia

Attach all routine monitors including pulse oximeter
Preoxygenate with 100% O ₂
Begin intravenous induction
Confirm ability to ventilate by mask
Administer intubating dose of a nondepolarizing muscle relaxant
Tape eyes shut
Remove pillow from underneath occiput
Ventilate with 100% O ₂ until onset of neuromuscular blockade
Administer additional induction agent or volatile anesthetic as required
Insert bite block to protect fiberoptic
Insert fiberoptic into mouth under direct vision
Retract tongue by providing jaw thrust if necessary
Visualize vocal cords and pass fiberoptic to carina under direct vision
Advance endotracheal tube along fiberoptic through cords
Confirm successful intubation by:
• visualizing carina through endotracheal tube with fiberoptic
• auscultating for bilateral breath sounds
• documenting presence of CO ₂ in expired gas

is administered for muscle relaxation. Such agents are chosen rather than succinylcholine because the duration of action of succinylcholine may be inadequate to allow completion of fiberoptic-guided endotracheal intubation by the beginning trainee.

The pillow beneath the head is removed and the patient is hyperventilated with 100% oxygen, with or without the addition of a volatile agent. If a volatile agent has not been delivered, an additional dose of intravenous induction agent is administered prior to insertion of the fiberoptic into the oral cavity. An O-ring bite block is utilized to prop the mouth open and prevent damage to the fiberoptic. Oral intubating airways are not employed. Anterior jaw thrust is initiated or the tongue is wrapped with gauze and gently retracted to maintain maximal pharyngeal opening.

Typically, the resident and instructor observe the procedure on a video monitor via a chip camera attached to the fiberoptic head. Alternatively, a teaching attachment (beam splitter) can be affixed to the fiberoptic head. Practically speaking, use of the teaching attachment dramatically reduces the amount of light available and makes visualization of anatomic landmarks difficult for both the endoscopist and instructor. Substitution of the exceptionally bright, but significantly more costly, xenon light source for the

conventionally employed halogen unit permits satisfactory use of the teaching attachment.

To record the progression of learning, timing of the procedure is begun when the fiberoptic is first inserted into the oral cavity and continues until the first breath is delivered via a successfully placed endotracheal tube. Confirmation of correct placement of the endotracheal tube into the trachea is made by visualization of the carina via the fiberoptic, auscultation of bilateral breath sounds, and the presence of carbon dioxide in expired gas as demonstrated by capnometry.

Antisialagogues are not routinely administered to patients with normal airways who will be intubated with the fiberoptic as part of the teaching program. Intolerable xerostomia as well as unnecessary and potentially undesirable tachyarrhythmias can result. However, glycopyrrolate is routinely administered when dealing with an anticipated difficult airway that will be managed in the awake state. In this situation, topical local anesthetics will be applied to the mucosa of the oral pharynx and glottis. Secretions act as a physical barrier preventing contact of local anesthetics with the mucosa. Consequently, secretions predispose to inadequate airway anesthesia and are best eliminated prior to administration of local anesthetics.

Hints for Learning

Ideally, trainees should receive operating room instruction and feedback from experts. In most cases, this is simply not an option, but there is an alternative.

Enlist a Colleague. I recommend working with a "buddy" (anesthesiologist, surgeon, nurse) who is also interested in learning the techniques. Buddies assist each other during the early learning stages. Such an associate can provide valuable encouragement and serve as an extra pair of educated hands. Greater energy, enthusiasm, and commitment can be engendered by two people with a common goal than by a single individual working solo in a vacuum. The desired target, learning a new skill and achieving proficiency, is less likely to be ignored, postponed, or forgotten. Paired learning has been studied and validated in other educational endeavors. In any event, a second qualified individual should always be present to monitor the patient's vital signs and overall general status while the endoscopist is preoccupied with learning, maneuvering the fiberoptic, and intubating the patient.

Design a Cart. A rolling cart should be designed for fiberoptic-guided intubation, perhaps in combination with difficult airway equipment (Table 2). It should be stocked with materials commonly employed for preparation of the patient and used during the procedure. Organization and availability of necessary supplies and related equipment will aid in attaining success. Another advantage of such a cart is to protect the fibroscope from damage both before and after each patient use. The instrument is delicate. Dropping it from working height to the floor may result in catastrophic consequences. If left draped across the manufacturer's open storage case, the glass bundles in the instrument can be easily damaged if the metal rimmed case should accidentally close and crush the device. Many institutions have only one small-diameter fibroscope available, so damage to the scope eliminates its availability during overhaul. The cost of repairs can be prohibitive and turnaround time can be lengthy. To protect the scope, two vertically mounted plastic tubes may be affixed to the cart. One is used to store the unused, clean fibroscope and the other accepts the used scope prior to decontamination. Polyvinyl chloride or corrugated cardboard cylinders can readily be obtained for this purpose and are inexpensive to replace.

Educate Colleagues. Surgical colleagues and nurses should be educated about the procedure, including safety aspects and patient benefits. This will ensure greater cooperation and understanding during the period of learning. Learning fiberoptic-guided intubation should not delay the

operating room schedule or the start of any individual surgical procedure. After the induction of general anesthesia, it is permissible for surgical preparation of the patient to begin, while proceeding with fiberoptic intubation.

Practice Frequently with Appropriate Patients. Anesthesiologists should gain the majority of their early experience in patients after the induction of general anesthesia. Indeed, it would be unethical to practice fiberoptic-guided intubation on awake patients in the complete absence of clinical indications for awake intubation.

Patients who require nasal intubation for intraoral or other surgical procedures can also be intubated with fiberoptic guidance under general anesthesia. Of course, as with any nasal intubation, vasoconstrictor agents should be applied to the nasal mucosa to prevent or limit hemorrhage during initial passage of the fibroscope or endotracheal tube.

In the early learning phase, if the nares are patent, it is recommended that the nasal route be employed when a difficult airway is anticipated. Abnormalities in airway upper anatomy due to congenital deformities, acquired anatomic distortions from mass lesions, surgical procedures, traumatic injuries, or burns markedly increase the technical challenge. Success under these demanding circumstances will vary, depending on the operator's degree of manual dexterity, prior acquisition of requisite psychomotor skills, and perseverance.

Use Fiberscope in Evaluations. Additional valuable experience in handling the fibroscope in patients can be gained by using the instrument to visualize and evaluate the position and movement of the vocal cords prior to extubation after surgical procedures that may result in damage to laryngeal nerves. Examples include thyroidec-tomy, neck dissection, or carotid artery surgery. The scope can also be used to evaluate stridor following extubation or it may be passed down the endotracheal tube after suspected pulmonary aspiration. Additionally, confirmation of proper placement of either single- or double-lumen endotracheal tubes is readily achieved by direct visualization via the flexible fibroscope.

Of course, practice makes perfect. With repeated practice, the time required for first visualization of the larynx will dramatically decrease. In general, the amount of time devoted to learning and practicing the technique determines the ultimate achievement of clinical competence. Every clinician should be able to gain sufficient skills to increase the likelihood of success when

TABLE 2

Fiberscope-Guided Intubation Cart: Suggested Equipment

Equipment	Pharmaceuticals
Halogen or xenon light source	Lidocaine 4% solution
Fiberscope	Phenylephrine 0.25% commercially prepared
Oxygen cylinder/regulator and tubing	solution (or 1% ampules—dilution required)
Vertical tubes (2) to secure clean and used scope	Optional equipment
Gauze pads 4 × 4	Teaching head
Cotton batting	Video chip camera and monitor
Jackson cross-action forceps (Krause forceps)	VCR for recording
Atomizer	
Tongue blades	
Cotton tip applicators	
Nasal airways	
Bite block	
Syringes 10-cc	
Alcohol wipes	

caring for patients with anatomic airway aberrations and variations.

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Fiberoptics in Otolaryngology

STEVEN H. SACKS, M.D., F.A.C.S.

ADVANCES IN FIBEROPTIC TECHNOLOGY have profoundly affected diagnosis and therapy in the everyday practice of otolaryngology. Normal examination of the head and neck requires viewing of relatively deep and dark cavities. During routine examinations in the office, otolaryngologists use a monocular headlight to allow illumination of both anterior and posterior nasal cavity structures. This provides for excellent screening examinations of the nasal cavity and larynx.

The nasal cavity consists of a midline septum and three lateral wall turbinates (Fig. 1). The turbinates are surrounded by three spaces: the inferior, middle, and superior meati. Anterior and middle ethmoid and frontal and maxillary sinuses drain into the middle meatus. Pathologic changes are often apparent early in the middle meatus. Anterior rhinoscopy, performed with a monocular headlight and nasal speculum and preceded by administration of nasal decongestants, allows a limited view of the mid to posterior nasal cavity; the narrow middle meatus is almost impossible to examine in this fashion. In 1901, Hirschmann, utilizing a modified cystoscope, performed the first nasal endoscopy. His attempts were thwarted by poor illumination (1). In 1925, examination of the paranasal sinuses was described by Maxwell and Maltz. In 1978, after rigid fiberoptic scopes had been introduced into orthopedic and urologic surgery, Wigand and Messerklinger initiated the use of these scopes in examination of the nasal cavity and surgery of the paranasal sinuses (2).

Examination of the hypopharynx and larynx relies primarily on indirect mirror techniques. Many patients cannot be examined with this technique because they have hyperactive gag re-

flexes or anatomic variants, such as a large base of tongue or a posteriorly tilted epiglottis. In the past, any patient who could not be successfully examined by indirect laryngoscopy required direct laryngoscopy under general anesthesia. In the early 1970s, diagnostic fiberoptic pharyngolaryngoscopes allowed direct examination of the larynx in the office, decreasing the number of patients needing more invasive procedures.

Flexible Fiberoptic Laryngoscopy

Flexible fiberoptic laryngoscopes were first introduced in 1974 and gained almost immediate acceptance as an alternative method for office examination of the larynx when mirror techniques proved inadequate. The scopes consist of many light-carrying fiberoptic bundles approximately 4.0 mm in diameter and 30 cm long (1).

Examination begins with reassurance that the procedure is quick, safe, and painless. The nasal vault is first sprayed with 0.25% neosynephrine solution to produce vasoconstriction of the nasal mucosa and subsequent shrinkage of the nasal turbinates. This is followed by a 4% lidocaine spray. The fiberoptic scope is then coated with 2% lidocaine gel and passed through the nares. The patient is asked to breathe through the nose and the scope is passed just inferior to the inferior or middle turbinate and over the soft palate into the oropharynx. At this point, a panoramic view of the oropharynx and hypopharynx is generally achieved. Clear images of the vallecula, epiglottis, pyriform sinuses, and supraglottic and glottic larynx are obtained. Phonation and swallowing allow for observation of these dynamic processes.

The ability to view this area in a physiologic setting allows a multitude of diagnoses. One may identify a benign or malignant lesion of the mucosal surface. Fiberoptic laryngeal examination

From the Department of Otolaryngology, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029. Address reprint requests to the author at 1035 Fifth Avenue, New York, NY 10028.



Fig. 1. Coronal section of nose demonstrating relationship of nasal septum and lateral wall.

may reveal vocal cord paralysis or aspiration of secretions, suggesting decreased sensation in the larynx. Pooling of secretions in the pyriform sinus may suggest distal obstruction or neurologic dysfunction in the hypopharynx or esophagus. On many occasions I have used the scope as an aid in identifying and removing foreign bodies such as fish bones in the hypopharynx and larynx.

This scope is also useful in examining the nasal cavity. Examination of the nasopharynx may reveal enlarged adenoids, a nasopharyngeal mass, or palatal dysfunction leading to nasopharyngeal reflux or hypernasal speech. Patients often come to the office seeking help for chronic epistaxis. If the bleeding area is not obvious on anterior rhinoscopy, the scope can be introduced into the nose and the site of bleeding can usually be identified and treated. This technique has led to improved care of nasal bleeding and earlier diagnosis of otherwise occult tumors of the nasal cavity and paranasal sinuses. The fiberoptic scope is also useful in identifying early polypoid disease of the nasal cavity.

Fiberoptic scopes may be attached to videochips for imaging on monitors and recording on videotape for dynamic viewing as well as production of hard copies. Such images improve the documentation of abnormality and promote better patient understanding of the disease process. A stroboscope can be used as a light source. This

allows one to freeze the standing wave of the vocal cord in motion, often leading to a diagnosis after other means are not successful.

Functional Endoscopic Sinus Surgery

Both the maxillary and frontal sinuses drain into the hiatus semilunaris, a groove on the lateral wall of the nose (Fig. 2). The hiatus semilunaris begins anterior to the anterior ethmoid cells, initially traveling inferiorly, then swinging posteriorly beneath the anterior and middle ethmoid air cells. A partial medial wall, the uncinate process, originating anterior and inferior to the ethmoid bulba, bounds the hiatus semilunaris. The frontal sinus may drain directly into an anterior ethmoid cell or anterior and superior into the hiatus semilunaris via the nasal frontal duct. The maxillary sinus drains through its ostium into the posterior end of the hiatus semilunaris. Medially the middle turbinate overhangs this area. Taken together, all of these structures form the osteomeatal unit. Aberrations in the anatomy of this unit or swelling of the mucosa in this area may cause acute or chronic sinus disease (3, 4).

The scopes used for functional endoscopic sinus surgery (FESS) are rigid, measuring 4.0 mm in diameter, with viewing angles of 0, 30, 70, and 120 degrees (Fig. 3). This allows the surgeon to see around corners in the deep cavities that make up the nose and paranasal sinuses. These scopes offer a limited field of view, rendering valuable landmarks almost invisible.

The paranasal nasal sinuses are separated from the orbit by the lamina papyracea, from the

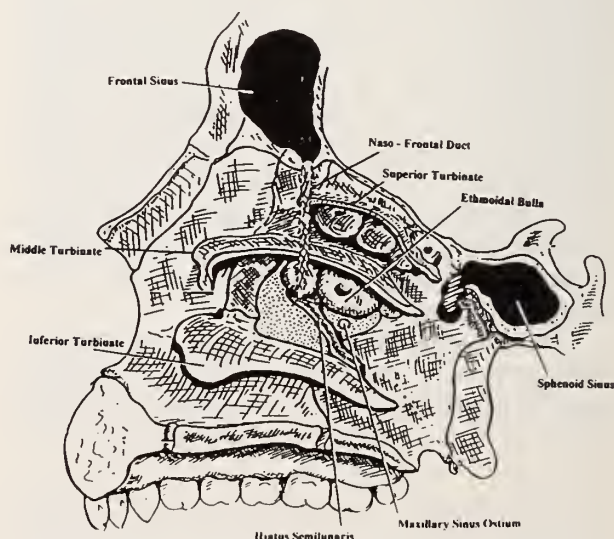


Fig. 2. Lateral wall of nose. Note that naso-frontal duct may drain into anterior ethmoid cell or hiatus semilunaris.



Fig. 3. Thirty-degree rigid fiberoptic scope.

brain by the cribriform plate, and from the carotid artery by the lateral wall of the sphenoid sinus. Each of these barriers is composed of thin bony walls. Intimate familiarity with this anatomy is crucial to avoid unintentional entry into other spaces. Numerous articles and editorials warn of the dangers of intranasal sinus surgery. In 1912, Mosher, an innovative head and neck surgeon, stated that "intranasal ethmoidectomy is one of the most dangerous and blindest of all surgical operations" (5). The 8% complication rate associated with FESS is probably inflated by many inexperienced surgeons (6). With proper training and identification of intranasal landmarks, this incidence should fall to less than 1%, the complication rate at The Mount Sinai Hospital and similar institutions (7–9).

One of the most sweeping advances that has taken place in otolaryngology in the past decade has been FESS. The ability to use fiberoptic scopes has allowed otolaryngologists to observe disease not previously appreciated and to operate on areas of the nasal cavity and sinuses that in the past could only be approached via an open procedure. With this tool has also come a rethinking of the etiology and treatment of sinus disease.

At The Mount Sinai Hospital, where intranasal surgery has been performed for 50 years, we have established the ethmoid sinus as the key to paranasal sinus drainage (7–9). Even chronic

frontal sinus disease often responds to intranasal ethmoidectomy without requiring an external approach. FESS has brought these findings to the mainstream of otolaryngology. Endoscopes have enabled the general otolaryngologist to be involved in the diagnosis and intranasal treatment of acute and chronic sinus disease.

In conclusion: fiberoptic technology has enabled the otolaryngologist to perform examination of the larynx and nasal cavity with greater detail, ease, and comfort to the patient. It has also helped to revolutionize the way otolaryngologists think about and care for paranasal sinus disease.

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Upper Gastrointestinal Endoscopy

JEROME D. WAYE, M.D.

UPPER GASTROINTESTINAL ENDOSCOPY is the technique of using an optical instrument to provide direct visualization of the gastrointestinal tract from esophagus through stomach, duodenal bulb, and descending duodenum.

History. Over 100 years ago, instruments with external illumination provided by candle offered limited views of the esophagus (1). Once the stomach was entered, steep angulations prevented further visualization. A semiflexible gastroscope (at that time called a "flexible gastroscope") was introduced in 1932 by Wolf and Schindler (1). The maximum flexion of this instrument, which had multiple lenses of short focal length, was approximately 30 degrees. Introducing the "flexible gastroscope" into the gastrointestinal tract required considerable skill and experience. As inflexible as this instrument was, it represented a quantum leap from the completely rigid "lead-pipe" configuration of previous devices. Semiflexible gastroscopes were associated with a high risk of patient discomfort and perforation. Their major limitations were inability to inspect certain areas of the stomach and to perform biopsy. The advent of fiberoptic rods that could bend light around corners created the impetus for the first flexible fiberoptic gastroscope, developed in 1957. It was first clinically used by Hirschowitz and colleagues (2).

Image Transmission

The introduction of fiberoptics revolutionized gastroenterology. Initial gastroscopes were cumbersome, dangerous, and uncomfortable for patients, whereas flexible fiberscopes with tip de-

flection capability were safe, easy to pass, and remarkably well tolerated.

The flexibility of fiberoptic instruments is directly related to the use of tiny glass rods which survive repeated bending without damage. Light entering one end of the fiber bounces internally during transmission to the opposite end, with only a small loss of light intensity. Each fiber has a glass coating of a different refractive index to minimize the loss of light and prevent "scatter" from one bundle to the next. When several bundles are spatially aligned, a single fiber will carry a spot of light from the field of view to enter the eyepiece in the same physical relationship to the object viewed. The image is created by transmission of thousands of individual points of light to create a mosaic of the original image. This technology has resulted in sufficient image quality to allow diagnostic accuracy. The number of glass fibers in each bundle approximates 20,000, providing superb resolution.

Early fiberoptic instruments were designed for visualization of the stomach, but not the esophagus. They offered a lateral viewing port, and illumination was provided by an incandescent bulb at the top of the instrument. Although flexible, they were incapable of tip deflection and air was insufflated into the stomach by compressing a rubber bulb.

Modern technology has developed current flexible gastroscopes with direct forward viewing to see the esophagus, four-way tip deflection to view the walls of the stomach, and a bending capability of 180 degrees. The instruments offer integrated air, water, and suction capability by depressing trumpet valves on the scope's head. Depth of field ranges from a few millimeters to over 10 cm. Incandescent light bulbs have been replaced by a separate fiberoptic bundle, which transmits light from an external high-intensity source, providing intense illumination of the

From the Department of Medicine, Mount Sinai School of Medicine (CUNY), and the G.I. Endoscopy Units at Mount Sinai Medical Center and Lenox Hill Hospital, New York, NY. Address reprint requests to the author at 650 Park Ave., New York, NY 10021.

stomach without generating heat within the organ.

Accessory instruments may be passed through the length of the gastroscope. These accessory instruments range from biopsy forceps, to snares for polypectomy, cautery probes for electrofulguration, laser light guides, and needles for injection. Accessories are generally passed through the suction channel, although some instruments provide two separate channels. The scope's external diameter has become smaller over the years; standard endoscopes are 8.5–11 mm in diameter, with a 2.8–3.2 mm suction-accessory channel. Modern flexible instruments accommodate a variety of recording equipment as an integral part of the scope or readily attached to the eyepiece, including still and video cameras. "Lecture scopes" consist of an adaptor with beam splitter, permitting the primary operator to look directly through the regular optical viewing system, while an observer monitors the procedure with another fiberoptic cable attached to a right-angle prism.

Within the last decade, video endoscopes have been developed which utilize a small charge-coupled diode designed to encode digitized information for a processor. The processor transmits an image electronically without the need for direct fiberoptic connections (3). The endoscopist and observers can view enlarged images on a video monitor instead of small images through an eyepiece. About 50% of the instruments currently sold throughout the world have video image capability. It is estimated that in the near future most endoscopes will use video technology rather than fiberoptic transmission.

Indications

A consensus statement by the American Society for Gastrointestinal Endoscopy (4) gives the following guidelines.

Diagnostic esophagogastroduodenoscopy (EGD) is generally indicated for evaluating:

Upper abdominal distress that persists despite an appropriate trial of therapy, or that is associated with symptoms or signs suggesting serious organic disease (e.g., anorexia and weight loss).

Dysphagia or odynophagia.

Esophageal reflux symptoms that are persistent or recurrent despite appropriate therapy.

Persistent vomiting of unknown cause.

Other system disease in which the presence of upper gastrointestinal (GI) pathology might modify planned management. Examples include

patients with a history of ulcer or GI bleeding who are scheduled for organ transplantation; patients who have had long-term anticoagulation or chronic nonsteroidal therapy for arthritis; and those with aerodigestive cancer of the head and neck.

Familial adenomatous polyposis.

Confirmation and specific histologic diagnosis of radiologically demonstrated lesions: (a) suspected neoplastic lesion; (b) gastric or esophageal ulcer; (c) upper tract stricture or obstruction.

Gastrointestinal bleeding (a) in most actively or recently bleeding patients; (b) when surgical therapy is contemplated; (c) when rebleeding occurs after acute self-limited blood loss; (d) when portal hypertension or aortoenteric fistula is suspected; (e) for presumed chronic blood loss and for iron deficiency anemia when the clinical situation suggests an upper GI source or when colonoscopy fails to identify an etiology.

When sampling of duodenal or jejunal tissue or fluid is indicated.

Cirrhotic patients in whom prophylactic sclerotherapy is considered.

To assess acute injury after caustic ingestion.

Sequential or periodic diagnostic EGD may be indicated (a) in patients requiring periodic surveillance of proven Barrett syndrome; familial adenomatous polyposis; (b) for follow-up of selected esophageal, gastric, or stomal ulcers to demonstrate healing; (c) in patients with prior adenomatous gastric polyps; (d) for follow-up of prior sclerotherapy or banding of esophageal varices.

Therapeutic EGD is generally indicated for:

Treatment of bleeding lesions such as ulcers, tumors, vascular malformations (e.g., electrocoagulation, heater probe, laser photocoagulation or injection therapy).

Sclerotherapy or banding of esophageal or proximal gastric varices.

Removal of foreign bodies.

Removal of selected polypoid lesions.

Placement of feeding or drainage tubes (peroral, percutaneous endoscopic gastrostomy, percutaneous endoscopic jejunostomy).

Dilations of stenotic lesions (e.g., with transendoscopic balloon dilators or dilating systems employing guidewires).

Palliative treatment of stenosing neoplasms (e.g., laser, multipolar electrocoagulation, stent placement).

Diagnostic EGD is generally not indicated for evaluating:

Distress that is chronic, nonprogressive, atypical for known organic disease, and is consid-

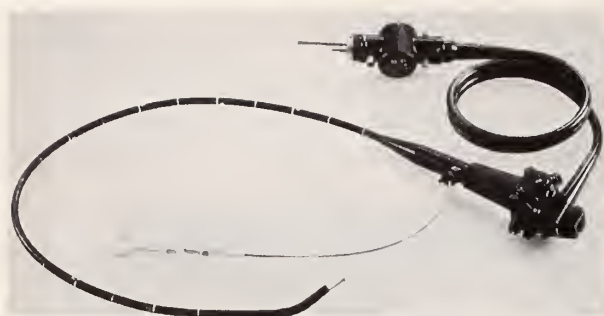


Fig. 1. Video gastroscope with biopsy forceps inserted through accessory channel. Portion that attaches to light source is coiled.

ered functional in origin (there are occasional exceptions in which an endoscopic examination may be performed once to rule out organic disease, especially if symptoms are unresponsive to therapy).

Uncomplicated heartburn responding to medical therapy.

Metastatic adenocarcinoma of unknown primary site when the results will not alter management.

X-ray findings of (a) asymptomatic or uncomplicated sliding hiatal hernia; (b) uncomplicated duodenal ulcer that has responded to therapy; (c) deformed duodenal bulb when symptoms are absent or respond adequately to ulcer therapy.

Sequential or periodic diagnostic EGD is generally not indicated for surveillance (a) for malignancy in patients with gastric atrophy, pernicious anemia, treated achalasia, or prior gastric operation; (b) of healed benign disease such as esophagitis, gastric or duodenal ulcer; (c) during repeated dilatations of benign strictures unless there is a change in status.

Contraindications

There are relatively few contraindications to gastroscopic examination. The most important contraindication is an uncooperative patient who remains so despite adequate premedication. Endoscopy under general anesthesia may be considered in certain circumstances; however, the additional risks must be weighed against the projected benefits of examination. The only other absolute contraindication to gastroscopy is coexistence of acute processes such as peritonitis or known bowel perforation.

Preparation for the Procedure

Upper gastrointestinal endoscopy is the most common type of endoscopic examination performed in the gastrointestinal tract. The procedure can be provided on an ambulatory basis and

is frequently accomplished in an office setting, at areas remote from the hospital. The only preparation required is a 4–6-h fast allowing time for the stomach to empty. Intravenous sedation is often used prior to gastroscopic examination, and a topical anesthetic spray or lozenge provides analgesia (5). In many areas throughout the world, esophagogastroduodenoscopy (EGD) is performed without sedation. The procedure is relatively rapid and usually well tolerated even without preendoscopic sedation.

Technique of the Examination

Following sedation, the patient is placed on the left side and a mouthpiece is inserted to prevent biting the instrument. Damaged instruments may cost several hundred to thousands of dollars for repair, depending on whether the bite through the flexible sheath has damaged vital control wires or image transmission bundles or permits water or fluid to enter internal portions of the instrument and short-circuit the electronics.

Most modern endoscopists advance the instrument under direct vision through the posterior pharynx, permitting visualization of epiglottis, vocal cords, and posterior pharynx during passage into the upper esophagus. Introduction under direct vision is the ideal method for advancing the instrument. Once the scope has entered the upper esophagus, air is insufflated and direct inspection of the lumen takes place throughout the esophagus, stomach, pylorus, duodenal bulb, and descending duodenum. An endoscopic examination of the esophagus, stomach, and duodenum can be performed in approximately 15–20 min. Biopsies can be taken as necessary. Still photography and video recordings are accomplished during continuous inspection of the mucosal lining (Fig. 1).

Complications

Complications of EGD are unusual (6). The overall incidence of complications during the diagnostic procedure is approximately one out of a thousand examinations. The major complications are perforation, bleeding, cardiopulmonary events, and medication reactions. Mortality is rarely associated with diagnostic procedures. Perforation of the esophagus or stomach occurs in 0.03% of cases (7). These usually occur in the presence of unexpected anatomic lesions such as stricture, carcinoma, or severe inflammatory changes. Occasionally, a perforation may occur in

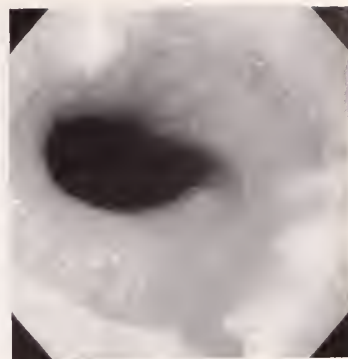


Fig. 2. Distal esophagus. Mucosal junction is well delineated; open hiatal orifice is seen.

the posterior wall of the pharynx during passage of the scope. When the instrument is passed under direct vision, such perforations are rare.

Significant bleeding rarely follows diagnostic upper intestinal endoscopy and is extremely unusual with biopsies taken by small cup-like forceps, which can be passed through the narrow instrument channel of flexible endoscopes. Gastric polypectomy, however, may be associated with significant bleeding. Cardiopulmonary complications have been reported in 0.8 per thousand examinations. The complications include pneumonia secondary to aspiration of gastric or pharyngeal secretions as well as blood.

Complications from medications include respiratory depression and cardiac arrhythmias. Hypoxia, as measured by pulse oximetry, is a frequently reported concomitant of the examination, but is not a true complication of EGD. Hypoxia is frequently due to oversedation, resulting in respiratory depression. Some hypoxia may be related to the size of the instrument in the posterior pharynx (airway), with larger-sized instruments resulting in a greater incidence of hypoxia.

Diagnostic Examination

The entire mucosal surface of the esophagus, stomach, and duodenum can be identified during gastroscopic examinations. Any irregularity, reflux of gastric contents, or active bleeding can be seen directly. Hiatus hernias are readily diagnosed, and dislocation of the cardioesophageal mucosal junction can be observed (Fig. 2).

A view of the entire stomach is readily obtained, but the upper portion just near the esophageal entry is not easily observed unless a U-turn maneuver (or retroversion) is accomplished with the endoscope. The retroflexed view is helpful for diagnosing hiatus hernia, tumors, gastric varices, and other abnormalities in this area. The endoscope is then passed down to the antrum and into the descending portion of the duodenum.

The pylorus is usually a tiny orifice through which all of the gastric contents flow into the duodenum. Gastric and esophageal peristalsis can be readily noted, and the absence of peristalsis may indicate involvement of the intestinal wall by an inflammatory or neoplastic process.

In the duodenum, views can be obtained of the duodenal bulb to inspect for evidence of ulcerations. Mild nonspecific upper gastrointestinal symptoms with or without weight loss require close inspection and biopsies to rule out villous atrophy, which would be indicative of sprue. Duodenal aspirates can be obtained for evaluation of infection with *Giardia lamblia* or for other abnormalities. Although a proper evaluation of small bowel and mucosal architecture was long considered to require a suction biopsy (with a dedicated tube designed for this purpose), it is now accepted practice to perform transendoscopic biopsies to diagnose malabsorption syndromes. Transendoscopic biopsies are currently the procedure of choice for histologic evaluation of mucosal architecture in the small intestine.

A hiatal hernia with continued reflux of acid may result in metaplasia of the distal esophageal epithelium so that the lower end of the esophagus becomes lined with columnar epithelium, a mechanism to protect acid-bathed portions of the esophagus with the more resistant gastric type of epithelium. Unfortunately, columnar epithelium that replaces squamous epithelium may also secrete acid, and ulcerations may form in the esophageal mucosa just at the area of the junctional epithelium. Replacement of esophageal by gastric mucosa in the tubular lined portion of the esophagus is termed Barrett syndrome. Although strictures may occur at the area of active inflammation, the most serious consequence is development of carcinoma in the columnar-lined esophageal segment. The incidence of carcinoma is higher in patients with Barrett syndrome than in the general population. Biopsies are recommended on an annual basis, to detect premalignant

nant changes of dysplasia in the columnar-lined segment (8). If high-grade dysplasia is present, the patient requires extremely close surveillance, and some have advocated surgical resection of the esophagus to prevent development of cancer. Displacement of the esophageal-gastric junction with a hiatus hernia does not have premalignant propensity. Recurrent acid reflux may produce stenosis of the esophagus, which requires dilation.

During endoscopy, ulcerations are readily evident and appear similar to "canker" sores in the mouth. They are usually white-based. A number of visual criteria can differentiate malignant from benign ulcers. Final confirmation rests with biopsy interpretation by the histopathologist. Among the most valuable aspects of upper intestinal endoscopy are the capability of taking directed biopsies from specific sites and the collection of cytologic brushings and smears. Most duodenal ulcers are associated with *Helicobacter pylori* infection, the presence of which can be observed on histopathologic examination of biopsies from the gastric antrum (9).

With the potent medications currently available for acid suppression, benign-appearing gastric ulcers probably do not require endoscopic reevaluation if the initial biopsies are negative for cancer (10). If ulcers are not healed on complete acid suppression, consideration should be given to surgical intervention.

Treatment Modalities

Gastroscopic examinations are frequently performed not only for diagnosis, but also for treatment of a variety of conditions affecting the upper gastrointestinal tract. Upper gastrointestinal endoscopy is an extremely useful modality for the control of bleeding from the esophagus, stomach, and duodenum. Bleeding from the esophagus is most commonly caused by esophageal varices related to portal hypertension. Conservative measures include balloon tamponade, which is transiently effective, but accompanied by a high incidence of early rebleeding. Endoscopic sclerotherapy has been found to be extremely effective in the emergency treatment of bleeding esophageal varices. Sclerotherapy can control acute variceal bleeding in over 90% of cases (11). Sclerotherapy is performed by injecting a substance into or around esophageal varices to promote intravenous thrombosis or to cause perivariceal inflammatory responses which effectively seal and block vascular channels. Sodium morrhuate, sodium tetradecyl sulfate, and ethanolamine are frequently used to sclerose venous channels. Chronic

sclerotherapy for obliteration of esophageal varices has not been shown to be significantly better than various surgical procedures aimed at decreasing portal hypertension.

Another modality has recently been introduced for the eradication of esophageal varices. This technique involves placement of small rubber bands on the varices, which gradually necrose from constrictive effects. They are applied to the varices with an integrated suction and banding device. Fibrosis of the wall results from inflammatory responses associated with pressure necrosis of encaptured tissue. The rubber bands are identical to those used for ligation of hemorrhoids and, in their nonstretched state, are approximately 2–3 mm in diameter. Banding has proven to be as effective for the management of acute bleeding as sclerotherapy, and as effective as sclerotherapy for the chronic ablation of varices (12, 13).

Bleeding, stricture, and perforation may result from injection of toxic material into and around esophageal varices.

Most gastroenterologists feel that acute bleeding from esophageal varices can and should be controlled by emergency sclerotherapy or rubber band ligation. Sclerotherapy is usually easier to perform than band ligation in the presence of major hemorrhage. Once hemorrhage is controlled, subsequent gastroscopies can be planned to obliterate varices by repeated sessions of either sclerotherapy or band ligation. Three to six treatment sessions are generally required to obliterate esophageal varices. In the presence of ongoing portal hypertension, varices recur in 5–10% of patients who have successful variceal obliteration.

Benign Stenosis of the Upper Intestinal Tract. Dysphagia, the sensation of delayed passage of food through the esophagus, does not occur until luminal narrowing reaches 12 mm or less. One of the most common causes for dysphagia and stricture in the esophagus is a Schatzki ring. A Schatzki ring is a circumferential web of tissue at the esophagogastric mucosal junction, which represents a "seam" between two different kinds of mucosa (Fig. 3). Hiatus hernia always accompanies this diagnosis. Symptoms are usually intermittent, but occasionally a food bolus becomes lodged at this narrowed segment, resulting in acute dysphagia. Typically, passage of a firm food bolus becomes blocked when a person is out to dinner, engaged in conversation, and does not chew food thoroughly. Consequently, this scenario is known as "steakhouse syndrome." Most patients learn that thorough chewing of food helps prevent dysphagia. A history of repeated



Fig. 3. Left Web-like benign structure at mucosal junction, typical Schatzki ring, on which food frequently gets caught.
 Fig. 4. Middle Linear streaks in distal esophagus depict ulcerations with distal stricture. This is severe reflux esophagitis.
 Fig. 5. Right Large, deep gastric ulcer in fundus of stomach.

episodes of dysphagia and acute symptoms are highly suggestive of the diagnosis. Endoscopic examination is usually curative, after the bolus is pushed through the narrowed segment or extracted through the mouth. If, however, the patient has a history of increasing dysphagia or a chronic history of dysphagia, it is not safe to attempt to push a foreign body through narrowed segments into the stomach. Pushing against a tight narrowing may result in perforation of the esophagus. Under these circumstances, the foreign body should be removed orally.

In the presence of peptic ulcerations or malignant stenosis, the lumen may be only a few millimeters in diameter (Fig. 4). Dilation may be performed by passing a flexible wire guide through the gastrosopic channel under direct vision. Upon removal of the instrument, the wire is left in place to safely permit subsequent dilations by passing hollow-core dilators of graded sizes over the guidewire with fluoroscopic control.

Stenoses that are not quite so narrow may respond to a special balloon placed through the instrument channel which, when inflated, will expand within the narrowed segment and dilate the stricture (14). Utilizing balloon technology, strictures in the pylorus or descending duodenum may also be dilated under direct vision. The most rapid and easiest way to dilate a wide stricture (such as present with Schatzki rings and some peptic strictures) is by introducing flexible bougies, which are available in graded sizes up to 60 French (approximately 2 cm in diameter). These are passed without fluoroscopic control following diagnostic endoscopy and do not require a guide wire or fluoroscopy.

Hemorrhage from Ulcers. Ulcers in the stomach may be caused by several factors, the most common being nonsteroidal anti-inflammatory drugs and acid-peptic digestion (Fig. 5). When ulcers bleed, upper gastrointestinal endos-

copy is the most effective technique for control of hemorrhage. Endoscopic treatment successfully controls hemorrhage in over 95% of actively bleeding ulcers. The various hemostatic modalities include laser; heat-producing cautery; and injection with agents to produce tissue desiccation, vasoconstriction, or large-volume tamponade. All the various techniques have a high degree of success in controlling spurting arteries and in preventing rebleeding (15). When EGD is performed after bleeding has spontaneously stopped, it is possible to use various endoscopic criteria to assess the prognosis. A red protuberance at the base of an ulcer crater, called a visible vessel, is associated with a high incidence of rebleeding. If, however, the ulcer base postbleeding is white and clean, the risk of rebleeding from that site is almost zero. The latter group of patients can benefit from early discharge. Those patients demonstrating normal vital signs and blood count may not require hospitalization. There has been recent interest in the ulcer of Dieulafoy, which can bleed massively (16). This is an erosion over an aneurysm that is usually situated in the upper portion of the stomach. The ulcer crater is not deep, and the small erosion may be extremely difficult to identify once bleeding has stopped.

Gastritis may be another cause for bleeding, although life-threatening hemorrhage is not often encountered. A specific type of gastritis is the so-called "watermelon stomach," where venous ectasias of the lower half of the stomach may be associated with portal hypertension, or can occur in the absence of any known etiology (17). Vascular ectasias are usually arrayed in linear radial-spoke-like patterns beginning at the pylorus and extending up into the midantrum. The name depicts the endoscopic appearance of the antrum with dark red vascular anomalies and contrasting normal pinkish intervening mucosa. The alternating dark and light colors are similar to those

of an end-view of a watermelon. Bleeding may be profuse and chronic from vascular ectasias.

Fascination with laser hemostasis, which a decade ago was greeted with enthusiasm, has now diminished. The laser is an extremely expensive and cumbersome machine. It is relatively immobile and cannot be transported to the patient's bedside, whereas other heat-producing devices or sclerotherapy needles are easily transportable anywhere in the hospital and are as effective as (or perhaps more effective than) laser therapy.

Various hemostatic agents can be injected into the ulcer base through long, flexible needles. These include epinephrine, hypertonic saline, saline (for tamponade purposes only), or small volumes of absolute alcohol to produce tissue desiccation. Injection therapy may be the easiest and safest method of treating emergency bleeding from ulcers in the upper gastrointestinal tract.

Although injection therapy is generally successful, some experts suggest a repeat endoscopic examination within 24 hr for purposes of reinjection at the previous bleeding site in order to ensure hemostasis.

Hemostasis can also be accomplished by a variety of heat-producing devices. Lasers generate heat within tissues, absent direct tissue contact. All the other cautery-like devices depend on a combination of pressure application and heat to stop bleeding and seal vessels. Bipolar electrodes generate heat by passing electric currents through a series of positive and negative electrodes, spaced at the tip of a tiny probe. The probe is passed through a biopsy/suction channel. When this device is applied on a bleeding site (or adjacent to it), heat is generated with a small depth of penetration. The heat/cautery effect seals the vessel. The use of pressure on a bleeding vessel with the cautery-heating probe stops the flow of blood through the ulcer bed and permits subsequent application of heat to seal vessels that have been pressed together (coapted) by pressure from the probe.

Heater probes are another thermal modality that can be passed through an endoscopic channel. This device heats up to 220 degrees in one-fifth of a second, creating a "branding-iron" cautery effect to seal blood vessels. All these modalities can be utilized in the stomach and duodenum.

Cancer in the Upper Intestinal Tract. Cancers of the esophagus and stomach have a poor overall prognosis. Endoscopes contribute to the diagnosis of carcinoma by providing tissue samples, assisting in control of bleeding, and establishing luminal patency. Transendoscopic snare

techniques are reported to cure some upper gastrointestinal cancers confined to the mucosa.

In the United States, there are only scattered reports of "early gastric cancer," but this type of malignant tumor is frequent in other parts of the world. Reports from Japanese and South American centers have revealed that early gastric cancer is quite prevalent and can be totally removed by endoscopy, as long as the tumor is confined to the superficial mucosa. The best results are in small, nonulcerated lesions (18). Early lesions may also be treated with laser or photodynamic therapy.

Obstructing cancers of the esophagus deemed incurable because of local or distant metastatic disease may be treated with a variety of endoscopic procedures aimed at luminal patency to permit swallowing of saliva and liquids. Frequently, resumption of a normal diet is achieved. Lasers have been successfully used for palliation of obstructing carcinomas in the esophagus by destroying the bulky tissue that impedes passage of both solids and liquids. Lasers may also assist in vaporizing tissue on the surface of tumors to control bleeding and decrease transfusion requirements. There have been some reports of decrease in tumor bulk from injection of absolute alcohol into malignant tissues. The mechanism appears to be partial necrosis of the tumor with widening of the lumen.

Stents may be placed through an inoperable obstructing esophageal cancer under endoscopic control. A variety of devices, called esophageal prostheses, are used to establish or maintain passage through malignant strictures. Some gastroenterologists prefer to make stents from soft malleable plastic for each individual patient, rather than to rely on fixed-length and fixed-diameter devices commercially available (19). Placement of stents requires considerable expertise, and patients must meet various qualifying criteria, one of which is inoperable disease, since the stent is only palliative. The criteria for inoperability may be based on the nature of the tumor (local or metastatic) or on the patient's general medical condition. The second criterion is morphologic, encompassing bulky and circumferential tumors. Stents have no mechanism for fixation in the esophagus and are anchored in place by a distal lip and a proximal flange. The distal lip prevents the stent from migrating up the esophagus, since it rests on the lower edge of the tumor mass. Its funnel-shaped flange on the upper end serves to direct food and fluid into the tubular opening and also prevents downward migration, because it is impacted on the upper edge of the tumor. The length

of each stent must be carefully chosen for individual tumors so that slippage of the prosthesis does not occur.

The most recent advance and one which holds great promise for dysphagia relief associated with inoperable esophageal carcinomas is a flexible metal expansile stent (20). This prosthesis consists of a collapsed cylindrical mesh of interlacing metal wires, which is delivered directly into the obstructing tumor. It gradually self-expands to a wide diameter over several hours. This circumvents one of the problems of inserting the more rigid plastic/rubber stents, which are fairly large (19). Most of the rigid stents are approximately 2 cm in diameter and require tumor luminal dilatation to their external diameter prior to introduction. During the dilation, perforation of the esophageal wall occurs in about 5% of patients. Although this is a serious complication, most patients respond to conservative medical management and can safely have stents placed subsequently.

Flexible wire-mesh stents circumvent the need for dilation. They are placed through the lumen of a narrowed esophageal tumor in a furled position, with the wire twisted tightly around a stiff introducing catheter. The introducing catheter is inserted under direct vision (or under fluoroscopic control) through the tumor, and when a protective sheath is removed, the stent gradually expands to a diameter of approximately 1 cm. This diameter permits relatively unimpeded swallowing and tolerance of most oral intake. Continued tumor growth through the wire-mesh stent reoccludes some lumina. This may be treated with dilations, placement of a second stent through the first one, laser ablation of the tumor in-growth, or balloon dilatation. Clinical trials are currently underway to deploy a sheathed stent to prevent tumor in-growth.

"BICAP tumor probes" are another treatment modality for obstructing esophageal tumors. They were introduced several years ago, but have not gained wide popularity. This device has alternating longitudinal strips of positive and negative electrodes that, when wedged into a tumor and activated, cause heat to flow between the alternating electrodes with resulting thermal tumor necrosis. Although placement of the probe can be monitored endoscopically, if the probe contacts normal esophageal mucosa, the resulting thermal damage may result in stricture formation in nontumor portions of the esophagus.

There has been recent interest in photodynamic therapy for inoperable cancer of the esophagus. This treatment involves intravenous ad-

ministration of a light-sensitive agent that concentrates within malignant tissues. On photoactivation, usually with a laser source, intense tumor necrosis ensues, with slough and tumor regression (21).

Gastric Polyps. Gastric polyps may range from tiny 1–2 mm tumors up to lemon-sized (Fig. 6). Most gastric polyps can be removed endoscopically, although it is only necessary to remove those which are problematic. Many gastric polyps are first discovered during investigation of anemia.

The majority of gastric polyps are not adenomas, but are hyperplastic. These latter polyps have no premalignant potential. If small and not the cause of symptoms or anemia, they may be left alone. Adenomas are considered to be premalignant lesions or may be markers of malignant tendency in the stomach (22). If the stomach contains multiple polyps, the tendency is for all of them to have the same histologic conformation. In order to ascertain their morphology, if the stomach contains many gastric polyps, a few should be removed for histologic examination; however, if only a few are present, they should probably all be removed. The removal of gastric polyps involves a technique similar to colon polypectomy, where the gastric polyp is encircled with a snare, electrocautery current is utilized to coagulate the blood vessels in its base, and the polyp is then removed through the mouth.

Gastric polyps that cause symptoms, anemia, or intermittently obstruct by prolapsing through the pylorus require removal. The size of the polyp that can be removed depends on the endoscopist's skill and experience.

Foreign Bodies. Most ingested foreign bodies may be readily removed by flexible endoscopic techniques. Foreign bodies, such as impacted fish bones located in the pharynx or cricopharynx, may be extremely difficult to remove because of the sensitivity of that area. General anesthesia may be necessary, and a rigid instrument, as used by otolaryngologists, may be more appropriate for manipulation of foreign bodies at that level. Flexible endoscopes successfully remove most objects in the body of the esophagus or in the stomach. An ingested foreign body less than 20 mm in diameter usually passes spontaneously through the pylorus and through the entire intestinal tract. Foreign bodies that are pointed at both ends (sewing needles) have a tendency to impact in the intestinal wall and should probably be removed by endoscopy or surgery. Most foreign bodies can be removed with a snare or a special basket-type retriever. The use of an overtube inserted into the

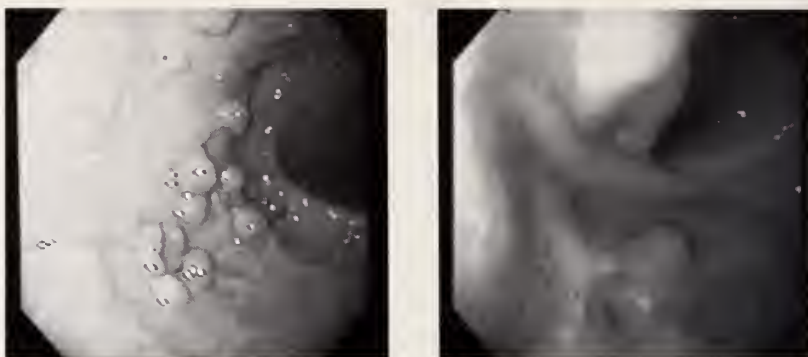


Fig. 6. Left Multiple benign gastric polyps. Fig. 7. Right Gastric view of percutaneous endoscopic gastrostomy. Feeding orifice is in center of star-shaped bumper.

esophagus for protection of the esophageal walls may be necessary for removal of open safety pins, razor blades, and other sharp objects.

Percutaneous Endoscopic Gastrostomy

Placement of gastrostomy feeding tubes has generally been viewed as a surgical technique. In 1970, Jeffrey Ponsky, a surgeon trained in endoscopy, developed a technique for placing feeding tubes in the stomach with the use of an endoscope (23).

With the gastroscope in the stomach, air is insufflated, which pushes the gastric wall against the anterior abdominal parietes. When the stomach wall opposes the abdominal wall, a needle can be placed percutaneously through the abdominal wall to pierce the gastric wall and enter the gastric lumen. The site for successful puncture is aided by transillumination of the endoscope's light through the abdominal wall. Once a hollow percutaneous needle has passed into the stomach, a long suture inserted through it is captured with a snare or grasping device introduced through the gastroscope. The suture is then withdrawn along with the gastroscope through the mouth. The suture which protrudes from the mouth extends down the esophagus, into the stomach, through the gastric wall, and across the abdominal wall to exit on the skin. A feeding tube with a tapered tip is attached to the suture near the mouth. By pulling on the end of the suture exiting from the abdominal wall, the entire length of suture, with its attached feeding tube is pulled through the abdominal wall and exits from the skin. A small skin incision of approximately 1 cm facilitates easy passage of the tapered tube through the skin and fascia of the abdominal wall. The feeding tube has a flared bumper at its other end, which prevents the tube from exiting the stomach and abdominal wall (Fig. 7). Reintroduction of the gastroscope allows precise placement of the internal bumper flush against the gastric wall. Apply-

ing tension on the external portion of the tube ensures that the gastric wall lies against the abdominal wall, and that position is fixed by a retaining ring placed onto the feeding tube at the skin, which prevents slippage. A seal quickly forms between gastric wall and anterior abdominal parietes so that a fistulous tract is formed in 7–14 days. The tapered end is cut from the feeding tube and intragastric feedings can be started almost immediately. The risks of such a procedure are minimal and include infection or puncture of an adjacent viscus. PEG can be performed within 30 min by a team of two operators, which usually consists of one physician and one trained endoscopic assistant.

Endoscopic Ultrasound

An ultrasound probe has been developed for incorporation into an endoscope tip. This probe permits ultrasound waves to be transmitted from a minigenerator at the end of the scope. The ultrasound image is displayed on an external monitor from any location in the esophagus, stomach, or duodenum. Images are detailed and clear. With its exquisite sensitivity, the layer from which a tumor arises is readily identified. One example is a leiomyoma arising from the muscularis propria. It is also possible to detect a malignant tumor's depth of penetration and extension into muscular wall as well as beyond, into adjacent structures such as blood vessels. Lymph nodes adjacent to the intestinal tract can also be delineated with this technique.

In addition to accurately staging tumors and determining operability (24), since invasion of adjacent organs can be seen and lymph nodes can be demonstrated, this modality is extremely useful to differentiate submucosal lesions in the intestinal tract, such as lipomas, leiomyomas, gastric varices, or extrinsic masses compressing the intestinal tract. The technique is relatively new, but has been shown to be more accurate than external ultrasound and computed-tomographic

scan for staging of malignant tumors of the esophagus, stomach, duodenum, and pancreas (25).

Summary

Upper intestinal endoscopy is a well-accepted method for evaluation of the esophagus, stomach, and duodenum. The techniques are standardized and extremely safe. The therapeutic capability for control of gastrointestinal hemorrhage is a major advance in the treatment of gastrointestinal bleeding. Endoscopic ultrasound is useful in the staging of upper intestinal malignancies. Above all, the ability to directly visualize the mucosal lining, to obtain biopsies, and to remove polyps has made endoscopy a primary tool for investigation of upper gastrointestinal pathology.

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Grand Rounds In Dermatology

Case 1-1994

From the Weekly Grand Rounds of the Department of Dermatology at The Mount Sinai Hospital

CYNTHIA GERARDI, M.D., AND MARK G. LEBWOHL, M.D.

Case Presentation Cynthia Geradi

THE CASE of a 44-year-old woman with a 27-year history of skin lesions on the neck was presented at The Mount Sinai Hospital Dermatology Grand Rounds. She was complaining of a recent increase in skin lesions involving the face.

The skin lesions on the neck were first noted following an automobile accident at the age of 17. The patient does not have a history of atherosclerotic vascular disease, cardiac valvular disease, a bleeding diathesis, or visual symptoms. There is no family history of similar skin lesions or visual abnormalities.

On physical examination the patient had yellow papules and plaques involving the neck, axillary folds (Fig. 1), antecubital fossae, periumbilical area, and inguinal folds. There were also yellow macules on the mucosal aspect of the lower lip (Fig. 2). On fundusoscopic examination, each eye had angioid streaks coursing through the papillomacular bundle and some atrophy at the margins. There was no subretinal hemorrhage or detachment. On cardiac auscultation there was a I/VI systolic murmur. The remainder of the patient's physical examination was unremarkable.

Skin biopsy from the neck revealed fragmentation and clumping of elastic fibers which are calcified in the middle and deep dermis.

Diagnosis: Pseudoxanthoma elasticum (PXE)

Discussion

Raul Fleischmajer: Would anyone like to comment from a clinical viewpoint?

Mark Lebwohl: The basic defect in pseudoxanthoma elasticum (PXE) is an aberrant calcification of elastic fibers in the skin, retina, and cardiovascular systems. In mild cases one sees isolated yellow papules involving flexural skin, including the neck, axillae, umbilicus, inguinal region, and antecubital fossae. In more extensive cases the papules become confluent and one sees redundant folds of skin. The most common site is the neck, followed by the axillae.

One reason this disease has major significance is that it is associated with the development of angioid streaks (Fig. 3), which are calcified cracks in Bruch's membrane, an elastic tissue-containing membrane that separates the vascular choroid from the retinal pigment epithelium. A proportion of PXE patients go blind; in many cases, this complication is preventable.

Calcification of the internal elastic lamina of arteries results in gastrointestinal bleeding as well as bleeding from other sites. Accelerated heart disease and cardiac valvular disease are additional complications.

Steven Kurtin: There have been case reports of patients with myocardial involvement and an-

Adapted from the authors' Grand Rounds presentation at The Mount Sinai Medical Center on November 10, 1994. From the Department of Dermatology, The Mount Sinai School of Medicine, New York, NY. Address reprint requests to Mark Lebwohl, M.D., Department of Dermatology, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1049, New York, NY 10029.

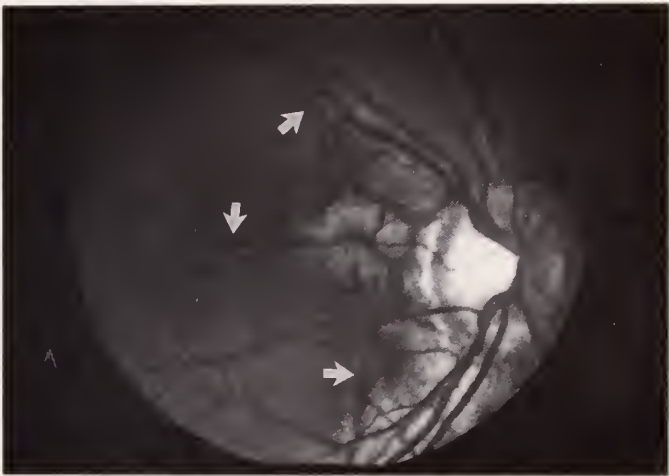


Fig. 1. Above Yellow plaques forming redundant folds of skin in patient's axilla.
Fig. 2. Top right Yellow macules on mucosal aspect of lower lip extending to gingival mucosa.
Fig. 3. Bottom right Angioid streaks (arrows).

gioid streaks without apparent skin involvement. I am curious whether some patients with gastrointestinal bleeding may have mucosal involvement but have no apparent skin manifestations.

Mark Lebwohl: That is an excellent point. We have reported on patients presenting with myocardial infarctions because they had calcification of the coronary arteries, yet no clinical evidence of skin involvement; however, random biopsy of the apparently normal skin of the neck or axillae or a scar has revealed the characteristic histologic findings of PXE.

We have also made the diagnosis of PXE in patients without skin lesions by biopsying the lip. Notice in the case presented here the dramatic and characteristic yellow papules on the inner aspect of the patient's lower lip (Fig. 2).

In addition, there are patients who have had years of gastrointestinal bleeding and were later found to have PXE. In fact, when bleeding is re-

current and no other cause is apparent, one must consider that PXE may be responsible.

The mucosal lesions are clinically and histologically similar to the skin lesions and can be demonstrated by appropriate endoscopic methods on the inner aspect of the lower lip, in the rectum and vagina, and in the stomach and bladder.

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Hepatic Hydatid Disease in Iran, with Review of the Literature

BAHAR BASTANI, M.D., AND FARROKH DEHDASHTI, M.D.

Abstract

We retrospectively reviewed 126 surgically proven cases of hydatid cyst of the liver selected from medical records of patients diagnosed clinically over the eight-year period 1972 to 1980. Sixty percent of the patients were in the third and fourth decades of life. The most common initial complaint was either right upper abdominal pain or a sensation of fullness, generally for more than two months. One or more cysts were more apt to be in the right lobe, and were subject to infection, rupture, or fistula formation. In 6% of patients, other intraabdominal cysts were found during surgery. In a few patients, the plain abdominal radiographs revealed curvilinear calcification. Upper gastrointestinal barium studies showed extrinsic pressure on the stomach or duodenum. Chest radiographs occasionally showed elevated right hemidiaphragm, right lower lobe infiltrate/atelectasis, right pleural effusion, and a pulmonary hydatid cyst. Liver-spleen scintigraphy often revealed a space-occupying lesion, but there were discrepancies either in number or location of cysts when compared with the surgical findings. All angiographic results were abnormal. Patients with infected cysts differed from the rest by a more common history of fever, and a greater incidence of right pleural effusion on chest x-ray.

Literature on pathophysiology, radiologic findings (including CT scan and ultrasonography), and surgical and medical therapy of hydatid disease of the liver is reviewed.

HYDATID DISEASE has a worldwide distribution; in sheep and cattle-raising countries it is an epidemic problem. There are two main forms of the human disease. The more common form, cystic hydatid disease, is due to *Echinococcus granulosus*, a 4–6 mm long tapeworm which infects the small intestine of the dog. The eggs, which are released in the infected dogs' feces, contaminate the vegetables which are ingested by sheep and cattle. The hatched embryos pass through the intestinal mucosa and into the portal circulation. The majority of the embryos are caught in the liver; others are caught predominantly in the pulmonary circulation, and a few end up in all the

remaining organs. In these organs the embryo develops into a cyst. The life cycle of the parasite is completed when the infected sheep or cattle (intermediate host) are slaughtered and dogs (definitive host) eat the viscera which contain the larval form. The larva subsequently develops into an adult tapeworm in the dog's intestine. Humans are the accidental intermediate hosts who are infected by a route similar to that in sheep and cattle: ingestion of contaminated vegetables or close contact with infected dogs. The incidence of hydatid disease has been high in the Middle East, South America, Australia, New Zealand, Japan, the Philippines, Northern China, and around the Mediterranean and the Baltic Seas (1–3).

In Iran, hydatid cyst is prevalent in most parts of the country, especially in the rural areas where offal from slaughter houses is not carefully disposed of, or where slaughtering is practiced on farms. A survey in the west of Iran in 1973 showed that 16 of 34 stray dogs, 28 of 55 sheep, and 12 of 116 cattle were infected (4). The average

From the Departments of Medicine (BB) and Radiology (FD), School of Medicine, Shiraz University, Shiraz, Iran. Address reprint requests to Bahar Bastani, M.D., Assistant Professor of Medicine, Department of Medicine, St. Louis University Medical Center, 3635 Vista Avenue at Grand Boulevard, P.O. Box 15250, St. Louis, Missouri 63310

figure for infected stray dogs in the epidemic countries has been estimated to be about 30% (1).

With the increasing ease of travel and migration, the disease, usually contracted in early childhood, is now being encountered in immigrant adults in many parts of the world in which it is not epidemic. Thirty-seven of 40 patients diagnosed and treated for hydatid cyst of the liver in Toronto General Hospital, and 22 of 24 in southern California, were immigrants (5, 6). Thus, general physicians, surgeons, and interventional radiologists practicing in nonepidemic areas need to be familiar with the diagnostic and therapeutic dilemmas of this disease.

Methods

We studied 126 patients with hydatid cyst of the liver operated on at the affiliated hospitals of Shiraz University School of Medicine (formerly Pahlavi University), Shiraz, Iran. This medical center is the major referral center of Fars, a southern province bordering the Persian Gulf, with a population of about 2 million at the time of the study. Because of tribal migration and rural customs, hydatid disease has remained one of the major community health problems in this region.

Data collection was based on retrospective review of the medical records of patients with clinical diagnosis of hydatid cyst of the liver over the eight-year period 1972 to 1980. Only the patients with surgically proven disease (including pathologic diagnosis) were included in the study. All of the radiographs were reviewed by the authors.

Results

During an eight-year period, 126 patients were diagnosed and surgically managed for hydatid cyst of the liver. The youngest patient was 7 years old (Table 1).

The most common initial complaints were

TABLE 1
Demographic Features, 126 Patients with Hydatid Cyst

	n (%)
Sex	
Males	67 (53)
Females	59 (47)
Age (years)	
<20	27 (21)
20–29	44 (35)
30–39	30 (24)
40–49	15 (12)
50–59	6 (5)
≥60	4 (3)

right upper quadrant pain or sensation of fullness. The longest duration of initial symptoms was 8 years (Table 2). Among the laboratory tests, alkaline phosphatase (normal value <4 Bodanski units) was abnormal (range, 4.5–28; mean $\pm$ SE, 13 ± 2) in 32%. Other liver enzymes (SGOT, SGPT, LDH) were frequently normal, as was the complete blood count. The erythrocyte sedimentation rate (ESR) was done too infrequently to be evaluated. The serological diagnostic tests were not routinely performed.

Radiologic Findings. Frequency of abnormal radiologic findings are shown in Table 3. Eight patients also had hydatid cyst in their lungs; in five of them the cyst was in the right lung, in two of them in the left lung, and in one it was mediastinal.

All of the patients had undergone surgery as detailed by Saidi (1). Surgical findings (Table 4) included other cysts found during laparotomy (2 spleen, 1 common bile duct, 1 kidney, 1 cecum). Two patients had concomitant cirrhosis of the liver.

Patients with infected cysts had a more frequent history of fever and abnormal chest radiographs resulting from a higher incidence of right pleural effusion (Table 5).

Discussion

The liver and the lungs are the organs most frequently involved with hydatid disease. The liver is reportedly involved in 75%, the lungs in 15%, and other organs in 10% of patients (1). In the present group, 73% had a single hepatic cyst.

TABLE 2
Initial Signs and Symptoms and Their Duration

	n (%)
Signs and Symptoms	
Right upper quadrant abdominal pain	93 (74)
Right upper quadrant sensation of fullness	65 (51.5)
Both of the above	43 (34)
Fever	33 (26)
Jaundice	33 (26)
Anorexia	13 (10)
Weight loss	10 (8)
Vomiting	9 (7)
Itching	6 (5)
Duration	
<10 days	12 (9.5)
<1 month	32 (25.5)
1–2 months	16 (13)
2–12 months	28 (22)
>12 months	49 (39)

TABLE 3
Radiographic Findings

	n (%)
Chest radiograph	109
Elevated right hemidiaphragm	25 (23)
Right pleural effusion	13 (12)
Coexistent pulmonary cysts	8 (7)
Right lower lobe atelectasis/infiltrate	5 (4.5)
Abdominal radiographs (obstructive series)	82
Hepatomegaly	19 (23)
Curvilinear calcification in liver	18 (22)
Splenomegaly	4 (5)
Air fluid level in hepatic cyst	2 (2.5)
Upper gastrointestinal barium studies	42
Extrinsic pressure on stomach/duodenum	17 (40.5)
Barium enema	6
Extrinsic pressure on hepatic flexure	4 (67)
Liver-spleen scintigraphy	48
Space-occupying lesion(s)	40 (83)
Discrepancy with surgical finding	12 (25)
Angiography	12
Cystic lesion	12 (100)

In two-thirds, the cyst was located in the right lobe. In the remainder, either the cyst was in the left lobe (19%) or one or more cysts were found in each lobe (13%). This distribution has been reported previously (5–8).

We noted that 60% of our patients were in their third or fourth decade of life, whereas the disease is most often acquired in childhood. This is in agreement with the previous reports (1, 9). Our findings (Table 1) are similar to the two reports from North America (5, 6). Symptoms usually occur when the cyst is large enough to compress or stretch pain-sensitive structures or interfere with their function, or when there is a complication such as rupture of the cyst into the biliary tree or its superinfection.

TABLE 4
Surgical Findings in 126 Patients with Hydatid Cyst of Liver

	n (%)
Number of cysts	
Single	92 (73)
Multiple	34 (27)
Location of cysts	
Right lobe	86 (68)
Left lobe	24 (19)
Both lobes	16 (13)
Concomitant extrahepatic intraabdominal cysts	8 (6)
Complicated cysts	
Infected	36 (29)
Communication with biliary tree or pleura	12 (9.5)

About one third of our patients had elevated serum alkaline phosphatase levels. This prevalence is similar to that reported by others (5, 6). These latter reports also documented elevated total bilirubin in 9%–20%, SGOT in 15%–21%, SGPT in 27%, and high eosinophil counts in 24%–43% of patients (5, 6).

Diagnosis. Plain radiographic features of hydatid cyst of the lung have been described in detail by Vessal et al. (10). Hydatid cyst should be suspected if there is evidence of a space-occupying lesion (SOL) in the liver. Plain abdominal radiograph may show calcification, hepatomegaly, or pressure signs over the adjacent organs. Indirect evidence for the presence of an SOL in the liver is elevated right hemidiaphragm, right lung base atelectasis/infiltrate, or right pleural effusion. Incidental finding of a hydatid cyst in the lung suggests that the SOL in the liver is most probably of the same nature. In 22% of the plain abdominal radiographs of our patients, curvilinear or ring-like calcification in the liver was seen. This radiographic sign has been reported in 20%–85% of the cases (5, 6, 11–13). Daughter cysts may also calcify, producing multiple small rings of calcification. Generally it is believed that calcification indicates death of the cyst and scoleces (1); however, in one report viable scoleces were found in three surgically treated patients with calcified cysts (12). Hepatomegaly has been reported in 15% (13) and was present in 23% of our cases. The water-lily sign, said to be created by floating daughter cysts and undulated detached endocyst on the surface of the fluid level, was not seen in any of our patients.

Rupture of the cyst through the diaphragm can produce pleural effusion or bronchobiliary fistula. The latter is best shown by hepatobiliary scintigraphy (^{99m}Tc -HIDA) (14). Concomitant presence of pulmonary hydatid disease has been reported in 27% of patients (15), and was present in 7% of our patients. Hydatid cysts produce focal defects in liver-spleen scintigraphy in over 90% of patients (16, 17). Despite the nonspecific nature of such defects, they are highly suggestive of hydatid disease in epidemic areas (1). Hepatic arteriogram performed in 12 patients demonstrated typical but not pathognomonic angiographic features, which included vascular displacement around an avascular mass. A thin peripheral halo of greater density was seen due to accumulation of contrast material in the more vascular pericyst. The halo is indicative of viability but its absence does not imply death of the cyst (11).

Endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic chol-

TABLE 5
Findings in Patients with Infected and Noninfected Cysts

	Infected	Noninfected	P*
	n (%)	n (%)	
Frequency	36 (29)	89 (71)	
History of fever	19 (53)	11 (12)	<0.01
Duration of symptoms			
<10 days	5 (14)	6 (7)	NS
<1 month	13 (36)	19 (21.5)	NS
1–2 month	3 (8.5)	13 (14.5)	NS
>2 month	20 (56)	57 (64)	NS
Chest radiograph	32	77	
Abnormal	14 (44)	27 (35)	NS
Elevated right hemidiaphragm	6 (19)	19 (25)	NS
Right pleural effusion	8 (25)	5 (6.5)	0.02
Coexistent pulmonary cysts	4 (12.5)	4 (5)	NS
RLL atelectasis/infiltrate	2 (6)	3 (4)	NS
Abdominal radiographs (obstructive series)	30	52	
Abnormal	16 (53)	19 (36.5)	NS
Hepatomegaly	10 (33.5)	9 (17)	NS
Curvilinear calcification in liver	6 (20)	12 (23)	NS
Splenomegaly	0 (0)	4 (7.5)	NS
Air fluid level in hepatic cyst	2 (6.5)	0 (0)	NS

* P = Fisher's exact p-value, statistically significant at <0.05.

RLL = right lower lobe.

angiography (PTC) can be used in patients who have intermittent obstructive jaundice presumably due to the rupture of hepatic hydatid cyst and intermittent passage of daughter cysts and other cyst contents into the biliary system. This complication has been reported in 5%–15% of the patients (18, 19). In a recent series from Kuwait, cystobiliary communication accounted for 10% of the patients with obstructive jaundice as an initial symptom (20). The ERCP and PTC can establish the diagnosis by showing contrast material inside a ruptured cyst or daughter cysts in the cyst cavity or in the bile ducts (21–22). Despite the reports of uncomplicated accidental or intentional puncture of the hydatid cyst (23–29), the general recommendation is to avoid PTC, biopsy, or cyst puncture whenever the possibility of hydatid cyst exists. There are reports of anaphylactic reaction, fatality, and disseminated peritoneal hydatidosis following accidental cyst puncture or rupture (12, 26, 30).

Sonographic features of hepatic hydatid disease have been described in detail (15, 31, 32). Since ultrasound examination is easy, relatively inexpensive, noninvasive, and involves no radiation, it is considered by some to be the primary diagnostic technique in the investigation of hepatomegaly in epidemic areas (31).

The most common finding is an anechoic space with well defined borders and marked en-

hancement of the back-wall echoes indicating pure fluid collection (univesicular, uncomplicated hydatid cyst). There may be localized thickenings of the wall due to early stages of daughter cyst formation. There also may be a layer of fine echoes in the dependent part of the cyst cavity, exhibiting free movement with changes in the patient's position. This sign indicates that a large amount of free-floating hydatid sand (hydatid scoleces and brood capsules) is present in the cyst cavity, but is not pathognomonic.

The other sonographic feature of hydatid disease is fluid collection within a split wall. This happens when the endocyst (laminated membrane) is ruptured and separated from the outer pericyst layer with hydatid fluid in between. When the separation is more complete, the ruptured endocyst may appear as a floating membrane inside the cyst, a finding highly suggestive of hydatid disease. Multivesicular hydatid cyst (daughter cysts inside the mother cyst) appears as fluid collection with well-defined contour, divided by septa which are more or less thick and complete. A typical case may show the honeycomb picture. The multicystic appearance or cyst-within-a-cyst pattern is accepted as characteristic of hydatid disease.

Another sonographic appearance is a roughly rounded mass with irregular contour and mixed echogenicity. The mixture of hypo- and hyper-

echoic structures occurs when a multivesicular cyst is infected. Daughter cysts may still be identifiable in the larger cyst. When the hydatid cyst ruptures into the biliary tree, or becomes superinfected with gas-producing bacteria, the ultrasound examination may reveal the water-lily sign (32). Biliary obstruction may be suspected in the presence of intrahepatic biliary dilatation with dense echoes due to obstructing daughter cysts or fragments of the endocyst. The cysts which are totally calcified produce a nonspecific sonographic pattern of intense acoustic shadowing. In addition, ultrasound can identify clinically unsuspected cysts in the peritoneum or other intra-abdominal organs.

Like sonography, computerized tomography (CT) is useful in detecting hepatic hydatid cyst (11–13, 33–35). It clearly and precisely demonstrates the presence, number, size, and location of the cysts, as well as clues to the presence of cyst-related complications (that is, superinfection or rupture into the biliary system). The CT features of hepatic hydatid cyst include well-defined single or multiple cysts (univesicular or multivesicular due to the presence of daughter cysts). Calcification in the pericyst layer (curvilinear or nodular) not detectable on plain abdominal radiograph may be shown on the CT. Contrast enhancement accentuates the difference in density between the hydatid cyst and normal hepatic parenchyma. Rim enhancement due to hypervascularity of the pericyst is similar to the halo seen around the cyst on angiogram. Infected cysts have ill-defined borders, may contain air, or have layering (12, 35). Contrast enhancement of the surrounding parenchyma facilitates the detection of biliary dilatation due to obstructing daughter cysts or cyst debris (35). In a study of 50 patients with hydatid cyst of the liver, CT had a sensitivity of 98% (35). Isodensity of hydatid cyst and fatty liver resulted in a false negative test in one patient despite contrast enhancement.

Immunodiagnostic tests for hydatid disease include the intradermal Casoni test and several immunoserologic tests, such as complement fixation test (CFT), latex agglutination test (LAT), indirect hemagglutination test (IHA), enzyme-linked immunosorbent assay (ELISA), and immunoelectrophoresis (IEP) (5, 36–38). The serodiagnostic sensitivity of antibody detection methods ranges from 60%–90%. Patients with hydatid cysts in the liver are more likely to have a positive serologic test than those with cysts in the lungs or other organs (36). Lowest diagnostic sensitivity has been observed in patients whose cysts were intact (univesicular), whereas recently bro-

ken cysts have been associated with the most consistently detectable immune response (36). Children also have a lower incidence of seropositivity than adults. A positive intradermal Casoni test (test for immediate hypersensitivity) has been reported in 86% of surgically proven hydatid cysts of the liver (5, 36). Nonspecificity is considered the major limitation of this test, which has a 2%–45% incidence of false positive results (36). The IEP, based on visual identification of the *Echinococcus granulosus*-specific arc 5, has a sensitivity of 79% and specificity of 100% (36). The CFT at a dilution of 1/16 has a sensitivity of 84% and a specificity of 37%. The corresponding figures for ELISA are 94% and 65% (37). Others have reported sensitivity of 67% for CFT and 85% for IHA test (5). In countries in which parasitic diseases are more widespread, cross-antigenicity with other worms may give more false positive results. Note that a negative serologic test does not exclude, and a positive serologic test does not confirm, hydatid disease.

The reported incidence of grossly purulent cyst fluid ranges from 10% to 37% (19, 39). In general, patients with infected cysts had a higher incidence of fever, and more frequent abnormal chest radiographs resulting from a higher incidence of pleural effusion. In our experience, patients with infected hydatid cysts were, in general, less symptomatic than those with a true pyogenic abscess of a comparable size.

Treatment. Surgery remains the gold standard of treatment for hydatid cyst. Several different techniques have been described to deal with the residual cyst cavity after evacuation of the cyst contents (including the endocyst) and the use of various scolicalidal agents (1, 5, 7, 8, 40–51). The best approach to an uncomplicated hydatid cyst of the liver is evacuation, scolicalidal irrigation, and primary closure of the cyst. The scolicalidal agents commonly used are 0.5% silver nitrate, 15%–20% hypertonic saline, 80% ethanol, and 0.5% cetrimide. The preferred scolicalidal agent in our center is 0.5% silver nitrate, which has been shown to kill all scolices within two minutes (41).

The preferred surgical approach in our institution (1) is as follows. In brief, for simple (univesicular) cysts, the cyst area is completely isolated by inserting laparotomy pads moistened with 0.5% silver nitrate. Some hydatid fluid (about 1/5 of the estimated cyst volume) is aspirated through a 20 gauge spinal needle which is connected to a 3-way stopcock. An equal volume of 0.5% silver nitrate is then injected into the cyst cavity. After 5–10 minutes, the pericyst is incised and the cyst contents, including the endocyst, are

completely evacuated. The cyst cavity is again washed with 0.5% silver nitrate and palpated for detection of any other communicating cystic cavities or deeply located cysts bulging into the main cyst. Once the cyst is totally evacuated, the fibrotic portion of its wall is excised and a homeostatic running lock cat-gut suture is applied on the edge of the pericyst to prevent bleeding and biliary leakage. Subsequently, the cyst is closed with a continuous cat-gut suture and a Penrose drain is left under the liver. External drainage is used for infected cysts or those communicating with the biliary tract. Cyst excision is reserved for extrahepatic or peripherally located, resectable, intrahepatic cysts.

A recent trend favors the more radical surgical approaches of total or subtotal cystopericystectomy (39, 52–54). The former may be performed with or without preliminary controlled evacuation of the cyst contents (“open” or “closed” total cystopericystectomy). Closed total cystopericystectomy eliminates any risk of accidental fluid spillage or need for irrigation of the residual cyst cavity with scolicidal agents, which have caused serious complications (sclerosing cholangitis, acute pancreatitis, air embolism, anaphylactic shock, and severe acidosis) (1, 54–58). The use of formalin has been abandoned since it causes sclerosing cholangitis, severe systemic toxicity, and death (55, 58).

No single operation will suit all patients with hydatid cysts. Operative strategy should be tailored to the individual patient after an accurate preoperative evaluation of size, number, and location of the cysts, as well as interference with the biliary system or vascular supply of the liver (59). Unfortunately, surgical treatment of hydatid cyst is not without risks. The greatest threat is spillage of the cyst contents and dissemination of the hydatid disease. Local recurrence has been reported in 13% of the patients who were initially operated on for multivesicular hepatic hydatid cysts (51). All recurrences were diagnosed about five years after the initial surgery and required reoperation (51).

There have been recent reports of successful percutaneous aspiration of the cyst followed by cyst irrigation with hypertonic saline or 95% ethanol (27–29). All of these patients were treated prophylactically with mebendazole beginning several days prior to the procedure and continuing up to a month after the procedure in order to prevent possible complications from spillage of the cyst fluid. This method should be restricted to prospective studies of selected patients who cannot undergo surgery, or select not to have sur-

gery, and who have uncomplicated univesicular cysts.

Mebendazole and, more recently, albendazole have been reported to cause cyst shrinkage on serial ultrasound and CT scans, and result in improvement of the serological tests (60–65). These two drugs, broad-spectrum benzimidazole antihelminthics, act by inhibiting tubulin, leading to degenerative changes in the germinal layer of the cyst (66, 67). In a series of 37 patients treated with mebendazole, 35 showed evidence of cyst-cavity obliteration and no clinical signs of recurrence; 4 had histological proof of cure (62). On the other hand, a cyst which had lost its daughter cysts and had become diffusely echogenic while the patient was receiving mebendazole regained its pretreatment ultrasonic features and regrew, all of the daughter cysts reappearing within four months after a three-year course of therapy was completed (68). Therefore, reduction in size of the cyst and disappearance of daughter cysts does not necessarily indicate death of all scoleces.

Mebendazole is poorly absorbed and produces low plasma and cyst fluid concentrations; albendazole is better absorbed and achieves serum concentrations 10 times higher than an equal dose of mebendazole (69). Albendazole is quickly metabolized into albendazole sulfoxide, which is also therapeutically active. Mebendazole has generally been used in a dose range of 30–70 mg/kg per day, administered in 3–4 divided doses, but doses as high as 200 mg/kg per day have also been reported (61). Albendazole has generally been prescribed in doses of 10–14 mg/kg per day. Because of its higher efficacy and lower incidence of side effects, albendazole has replaced mebendazole in the treatment of hydatid disease. In a recent study comparing albendazole with mebendazole, the percentage of treatment success was higher with albendazole (43.5% vs. 26.6%) (70). Recent reports on albendazole have been encouraging, with a cure rate of 8%–33% and a total response rate of 53%–86% (69–73). The optimal duration of medical therapy has not been well established. Duration of treatment in the literature has ranged from a few months to several years.

Medical therapy also has been used for prophylaxis preoperatively (64, 74) and before and after therapeutic cyst aspiration (27, 28). In a large prospective study on 133 patients, preoperative treatment with mebendazole reduced the incidence of immediate postoperative complications (for example, secondary spread, infection, and fistula formation) from 14% in the untreated control subjects to 4% in the treated group (74). In another study, 10 of 11 patients treated with meben-

dazole for 25 days prior to surgery had no viable scoleces in their hydatid fluid at the time of surgery (64).

Medical therapy should be considered as an adjunct to rather than a replacement for surgery. It can be used prophylactically before surgery. In the case of inadvertent spillage during the operation, medical therapy should be continued for at least a few weeks postoperatively. Drugs as the sole mode of therapy should be reserved for the following situations: disseminated hydatidosis with no chance of cure by surgery, a patient who is not a good candidate for surgery, a cyst that is surgically unapproachable, or absence of adequate surgical facilities.

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Hepatic Hydatid Disease:

Current Surgical Treatment

BASIL C. GOLEMATIS, M.D., FACS, AND PANAYOTIS J. PEVERETOS, M.D., FACS

Abstract

In the 11 years 1980 through 1990, we performed a total of 273 operations for hydatid disease of the liver in 252 patients, including 35 patients who were over the age of 75 years. Cysts were multiple in 24.6%, calcified in 17.9%, and ruptured to adjacent viscera in 12.3% of cases. Ruptured cysts were small as well as large. Coexisting gallstone disease was found in 14.3% of cases. Reoperations for recurrence were performed in 6.4% of cases.

We believe that once the diagnosis is made, the treatment should be surgical, without regard to cyst size, the age of the patient, or the presence or absence of symptoms. Total pericystectomy, which eradicates the parasitic disease and thus minimizes the risk of recurrence, is the procedure of choice (17.3% in this series). When total pericystectomy is not feasible and the cysts are large and deeply placed, subtotal pericystectomy, in which only a small piece of the cystic wall is preserved, is a successful alternative (12.5% in this series). For complicated cysts, external drainage of the cystic cavity is necessary despite the known morbidity this procedure entails. In patients in this series undergoing external drainage, infection of the residual cavity and postoperative biliary fistula were the main causes of morbidity.

DESPITE various measures, the incidence of hydatid disease in Greece and other Mediterranean countries remains high (1, 2, 3). Because of political upheavals in the region and the emigration of Mediterranean people to countries around the world, hydatidosis is no longer uncommon in countries where the disease is not endemic (4). Thus hydatid disease is a concern for physicians worldwide.

Hydatid disease encompasses two morphologic and pathologic entities, the cystic form, caused by *Echinococcus granulosus*, and the alveolar form, caused by *Echinococcus multilocularis*. The second form accounts for only 1% to 2% of all cases of hydatidosis and is endemic only in certain areas, including Alaska, northern France, and Germany. In Greece only three cases of alveolar hydatidosis have been reported (in 1948, 1970, and 1974), and two of them have been treated surgically in our department.

Ultrasound and CT scanning are the current diagnostic tools, both having high diagnostic accuracy (5). The introduction of the parasiticide albendazole (6) has proved helpful in the prevention of recurrence but has undoubtedly not replaced the need for and the effectiveness of surgical treatment. The more radical surgical procedures available to eradicate the parasitic disease are not always feasible, and the recurrence rate is high. Complications of the disease remain severe and are not easy to treat effectively.

Patients and Methods

During the eleven years 1980 through 1990 a total of 252 patients with hydatid disease of the liver were operated on at the First Surgical Department of Athens University at Hippocraton Hospital.

Patients ranged in age from 15 to 84 years, and there was a slight female preponderance (120 male and 132 females); 35 patients were more than 75 years old.

In the reported period, 12 patients underwent

From the First Propaedeutic Surgical Clinic, University of Athens Medical School, Hippocraton Hospital, Athens, Greece. Address reprint requests to Panayotis Peveretos, M.D., F.A.C.S., 10, Herodotou St., 106 75 Athens, Greece.

TABLE 1

Preoperative Complications and Coexistent Pathologic Conditions in 252 Patients Operated on for Hydatid Disease of the Liver 1980–1990

	No. of patients	%
Age (patients > 75 years old)	35	13.8
Suppuration	17	6.7
Calcification	45	17.9
At least one prior operation for hydatid disease*	16	6.4
Multiple cysts	62	24.6
Coexistence of cholelithiasis	39	15.4
Rupture		
Into biliary tract	19	7.5
Into pleural cavity	6	2.4
Into abdominal cavity	3	1.2
Into alimentary tract	2	0.8
Into vena cava	1	0.4

* Operations performed prior to study period are not included.

two operations for recurrence of the disease, 3 patients underwent three operations, and 1 patient underwent four operations; thus, the total number of surgical procedures was 273.

Hydatid cysts were localized in the right lobe in 76% of cases and were multiple in 62 cases (22.7%). In 12 patients there occurred extrahepatic hydatid disease, either single or multiple, involving the lungs, the peritoneal cavity, the spleen, the kidney, the abdominal wall, or the bones. One 80-year-old patient had 13 cysts—3 in the liver, 5 in the peritoneal cavity, 4 in the lung, and 1 in the spleen. Liver cysts were totally or partially calcified in 45 cases (16.5%).

Suppuration of cysts, simulating liver abscess, was present in 17 cases (6.7%). Communication of the cysts with small biliary ductules, manifested by the presence of bile within the cystic cavity, occurred in approximately 65% of cases.

Frank rupture of liver cysts into the biliary tree occurred in 19 cases (7.5%) (Table 1).

Coexisting gallstone disease was found in 39 cases (15.4%). An urgent or early operation was necessary in 13% of patients, either for intrabiliary and intrathoracic rupture or for suppurated cysts.

Surgical Procedures

A right subcostal incision was employed in the majority of cases; a midline epigastric or left paramedian incision was also used. In a number of cases an abdominothoracic approach was used.

After careful exploration of the peritoneal

TABLE 2

Surgical Procedures and Mean Hospital Stay in 273 Cases of Hydatid Disease of the Liver, 1980–1990

	Cases	
	No. (%) N = 273	Mean hosp. stay, days N = 264*
Simple drainage	75 (27.5)	32
Cystectomy		
Partial	90 (33)	26
Partial, with omentoplasty	18 (6.6)	
Subtotal	34 (12.5)	16
Total	47 (17.3)	14
Hepatic resection	9 (3.3)	12

* Nine cases with postoperative complications and prolonged hospitalization are not included.

cavity and verification of the site, the size, the number, and the likely presence of cysts in other viscera, the operative field was isolated by packs soaked in povidone iodine solution or hypertonic saline solution; both solutions have scolical action and are used to avoid contamination of the peritoneal cavity by hydatid elements.

The operative procedures ranged from simple drainage to hepatic resection (Table 2).

Initially the cyst was punctured using a common large needle to confirm the diagnosis by aspiration of the characteristic hydatid content.

If neither closed total cystectomy nor hepatic resection was planned, the following procedure was undertaken.

At the site of initial puncture, a Mayo-Ochsner trochar was inserted to evacuate the entire contents of the cystic cavity. If the cyst was young and univesicular, the hydatid fluid was easily withdrawn. In such cases, removal of the whole laminated membrane was feasible after the prominent cystic wall was opened. In old cysts filled with daughter cysts or toothpaste-like material, spoons and forceps were used to remove the cystic contents.

After removal of all cystic contents, the remaining cavity was irrigated with the parasitocidal solutions mentioned above. Careful examination of the interior of the cavity was performed to identify other cysts, any small cysts communicating with the main cavity, and any hydatid debris. The eradication of all remaining known or suspected hydatid debris attached to the inner surface of the adventitia is mandatory. Omentoplasty, in which, after partial cystectomy, the remaining cavity is filled with a pedicled omental graft, was performed in 18 cases of uncomplicated cysts.

Obliteration of the cavity by suturing (capi-

tonnage or purse-stringing) was performed in most cases of uncomplicated cysts treated by partial cystectomy.

Total cystectomy may be performed without opening the cyst or by opening the cyst and evacuating the cystic contents. Meticulous ligation of all vessels and biliary radicles during dissection of the adventitia from the adjacent liver parenchyma is mandatory.

If the risk of damage of large vessels and biliary ducts does not allow complete extirpation of the cyst, a subtotal cystectomy is performed. After total or subtotal cystectomy, the liver parenchyma is lightly sutured using absorbable sutures. A drainage tube is always inserted in the remaining cavity after conservative treatment, or in the sutured area of liver parenchyma after total cystectomy or hepatic resection.

Results

The radical procedures of total cystectomy and hepatic resection were performed in 20.6% of cases, subtotal cystectomy in 12.5%. The conservative procedures—simple drainage of the cavity after evacuation, and partial cystectomy—were performed in 67.1% of cases (Table 2). Cholecystectomy was performed in 39 patients with gallstone disease, in 19 patients with cysts ruptured into the biliary tree, and in 10 cases in which the gallbladder was attached to the adventitia and its removal was necessary.

The complications requiring reoperations were subphrenic abscess, infection and suppuration of the residual cavity, hemorrhage, biliary peritonitis, and obstruction of the common bile duct by hydatid debris (Table 3).

Postoperative biliary drainage of long duration and infection of the remaining cavity after drainage were the main causes of morbidity. The average length of hospitalization in cases requiring drainage of the cavity was approximately 30 days; most of these patients were discharged with the drainage tube in situ. These patients were followed up at intervals of fifteen days. The duration of biliary drainage was longer than two months in nearly 10% of cases.

Hospitalization and period to recovery were significantly shorter after total or subtotal cystectomy or hepatic resection than after procedures that included drainage. (Table 2).

Mortality was 2.3% (6 patients), but only two deaths were related to the operation. One 80-year-old patient with liver cirrhosis and multiple liver cysts died on the second postoperative day from massive bleeding and concomittant hepatic

TABLE 3
Postoperative Complications Leading to Reoperation in 273 Cases of Hydatid Disease of the Liver, 1980–1990

	No. of cases
Subphrenic abscess	2
Suppuration of residual cavity	7
Hemorrhage	3
Biliary peritonitis	2
Common duct obstruction	6*

* In two cases, endoscopic sphincterotomy was used to remove hydatid debris.

failure, and another patient who had a suppurated cyst died on the tenth postoperative day from irreversible sepsis. The causes of death in the other four patients were renal or cardiac and pulmonary insufficiency.

Discussion

Hydatid disease is endemic in Greece, and approximately 400 new cases are operated on every year.

Hydatid liver cysts may remain asymptomatic for many years; once the diagnosis is made, the patient should be operated on. Neither the presence or absence of symptoms, nor cyst size, nor the age of the patient should affect this decision (7, 8). In our series, 35 patients who were older than 75 years of age required an urgent operation because of suppuration or rupture of the cyst. In our experience, even small cysts may rupture (8, 9). For these reasons, we do not support the concept that small cysts or cysts in patients over 65 years of age should be treated conservatively (10).

Calcified Cysts. Some authors recommend that calcified cysts causing no symptoms should be left alone (11). In our opinion only totally calcified cysts measuring no more than 3–4 cm should be allowed to remain without operation. For larger cysts, whether totally or partially calcified, surgical treatment is necessary because calcification does not preclude intrabiliary or intrathoracic rupture or other complications, including bacterial infection (5).

Preoperative Diagnosis. Among the preoperative diagnostic procedures a special emphasis must be placed on the contribution of computerized tomography in the choice of the proper operative procedure. The CT scan determines the exact extent of the lesion, the site of the cyst, and the number of cysts, and provides evidence of intrabiliary or intrathoracic rupture and the presence of hydatid disease in other organs (12) (Figs. 1, 2). CT scan is also likely to indicate the forma-

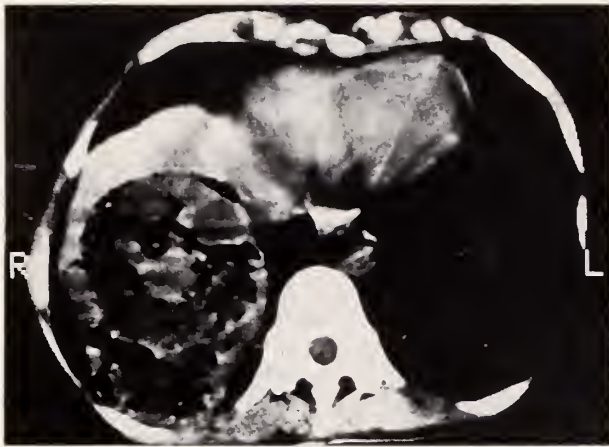


Fig. 1. Hydatid cyst affecting right lobe of liver has ruptured into pleural cavity.

tion of exogenous daughter cysts, which are the main cause of recurrence.

Ultrasonography is also helpful, but the subjective nature of interpretations makes this imaging method less valuable than computerized tomography.

Leaking. The cyst consists of two layers, the outer pericyst, which derives from host tissues, and the inner endocyst, which derives from the parasite. Intracystic pressure is higher than the pressure into the biliary tree and as the cyst grows, the endocyst breaks and allows the hydatid fluid to leak into the lower-pressure biliary ductules.

Small fissures exist in about 60%–80% of intact and uncomplicated cysts and are the cause of mild episodes of cholangitis and urticaria, which occur at intervals in most patients suffering from liver hydatidosis (8, 9, 13). With larger leaks, hydatid debris may pass and obstruct the bile ducts

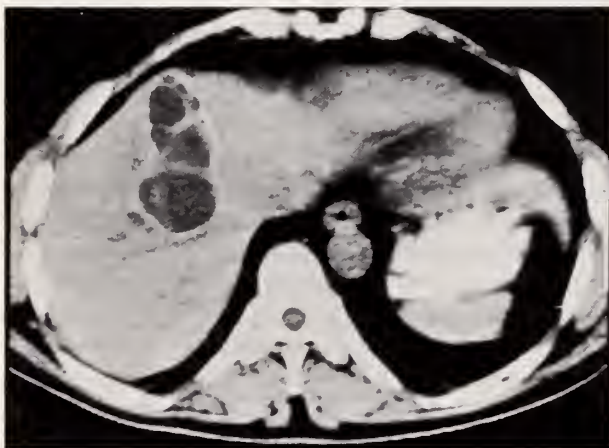


Fig. 2. In patient with obstructive jaundice, hydatid cyst in right lobe of liver has ruptured into biliary tree. Characteristic loss of round shape of cystic cavity is evident, showing that cystic contents have partially emptied into bile ducts, causing obstruction.

and the common bile duct. This frank rupture of cysts into the biliary tree, which occurs in 5%–25% of cases, is spontaneous and in a number of patients is the first evidence of the disease (14, 15).

The clinical picture, which includes colicky pain, obstructive jaundice, and cholangitis, closely simulates gallstone obstruction (16). Operative cholangiography (Fig. 3) and the characteristic CT scan and ERCP define the exact nature of common bile duct obstruction.

Suppuration of cysts takes place in 5%–12% of cases. The clinical picture resembles liver abscess, and urgent surgery is necessary. In our series, intrabiliary rupture and suppuration, each dictating an urgent operation, were found in 6.2% and 5.9% of cases respectively.

Recurrence. Reoperations for recurrence of hydatidosis are quite frequent. The incidence of recurrence has been estimated to range from 8.5% to 25% (17–19).

The causes of recurrence are peritoneal spillage and implantation during operations, new cyst formation from exogenous vesicles attached to the remaining pericyst after conservative treatment, and reinfection.

In the prevention of recurrence, the parasitocidal solutions we prefer are hypertonic saline solution and—above all—10% povidone iodine so-



Fig. 3. Preoperative cholangiography showing rupture of cyst into left hepatic duct, cutoff of left hepatic duct, and obstruction of common bile duct by hydatid vesicles.

lution. In our experience the latter may be infused within the cystic cavity without side effects even when a cystobiliary communication exists.

Encouraging results in the prevention of recurrence have been reported with the use of albendazole. This agent achieves high serum and cyst concentration of its principal metabolite, albendazole sulfoxide, an effective scolical agent that kills almost all scoleces within hydatid cysts (20).

Surgical Choices. Total cystectomy is the ideal procedure (7, 8, 21). It eliminates any exogenous vesicles covering the outer surface of the adventitia, a primary cause of recurrence (3).

Subtotal cystectomy is a successful alternative procedure. If the risk of damage to vital structures does not allow complete extirpation of the pericyst, the dissection is interrupted and a subtotal cystectomy is performed by preserving only those portions of the cystic wall that firmly adhere to liver parenchyma, so that the remaining cystic wall is as small as possible. Such a procedure avoids the longer hospital stays and the morbidity associated with conservative procedures.

When cysts are suppurated, when they are large and centrally placed, and when they occur in the upper and posterior area of the right lobe, pressing on the vena cava and the subhepatic veins, the physician must resort to more conservative treatment, such as drainage of the cavity after evacuation or partial cystectomy and drainage, even though these procedures have known morbidity and prolong the patient's hospitalization (16, 22, 23).

Suture obliteration (capitonnage), a resort mainly in cases requiring partial cystectomy (8), and omentoplasty (23) are additional procedures that reduce the remaining cavity. Omentoplasty has been documented to significantly shorten the hospital stay, but it should be avoided when cysts are infected.

The choice of hepatic resection (24, 25) for nonmalignant disease should be limited. Note that the remaining liver is highly likely to harbor additional smaller cysts that may grow postoperatively. In addition, the risk of reinfection is high, especially in countries where hydatid disease is endemic.

Cysts ruptured into the biliary tree should be treated by evacuation, partial cystectomy when possible, and drainage, followed by choledochotomy. After evacuation of hydatid elements from the biliary ducts, either side-to-side choledochoduodenostomy (14, 26) or external T-tube drainage are performed.

The choice of internal or external drainage depends on the operative findings. If the common bile duct is dilated, choledochoduodenostomy, which ensures the free passage of bile and of any remaining hydatid elements, is indicated.

If the width of the common bile duct is normal, T-tube drainage should be performed. Moreover, any remaining hydatid elements may be easily removed by endoscopic sphincterotomy (27).

The incidence of intrathoracic rupture is reported to vary from 1% to 4%. In these cases an abdominothoracic approach is necessary (8, 23).

Coexisting Cholelithiasis. In Greece, cholelithiasis coexisting with liver hydatid disease is found in 14%–17% of cases of hepatic hydatidosis (9).

Cholelithiasis coexists with liver hydatid disease in three forms: true hydatid lithiasis, parahydatid lithiasis, and accidental coincidence. In true hydatid lithiasis, histologic examination reveals the presence in the central part of the stones of hydatid elements that constitute the lithogenic nidus (9). Parahydatid lithiasis is attributed to the abnormal delay in passage of bile into the gallbladder provoked by an adjacent hydatid cyst.

In our experience surgical treatment of both diseases at the same time is the rule; exceptions occur in the rare cases of common duct obstruction either by stones or by hydatid debris, in which an initial endoscopic approach may be considered.

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THE MOUNT SINAI JOURNAL OF MEDICINE

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MARCH 1995

Issues in Medical Ethics

1. What Do We Owe People with Disabilities?
2. Science and Alternative Care

Daniel A. Moros, Rosamond Rhodes, and Allyson Robichaud, guest editors

From the Mount Sinai School of Medicine (CUNY)



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Introduction

DANIEL A. MOROS, M.D.
Associate Professor
Department of Neurology

ROSAMOND RHODES, PH.D.
Director, Bioethics Education

ALLYSON ROBICHAUD
Medical Ethics Fellow

Mount Sinai School of Medicine

THE SUBJECTS addressed in the eighth (1993) and ninth (1994) New York Regional Conferences in Medical Ethics, "What Do We Owe People with Disabilities?" and "Science, Alternative Care, and Third-Party Payers," represent complex challenges for our society. These issues are currently being vigorously examined and debated in government at the national, state, and local level. The results of the 1994 congressional elections make it clear that many of the previous assumptions underlying our government's involvement in the care of those struggling with illness and disability are now being questioned. And the mandate of the Food and Drug Administration to regulate the claims of medicine and alternative care is being challenged. Although the tone of the debates at both conferences was somewhat restrained, it seemed clear to us that these topics might soon receive more prominent attention because national opinion was uninformed and divided. We believe that government ought to be concerned with providing an acceptable minimum of health care, housing, nutrition, education, and transportation for all of our citizens, but we also realize that there are thoughtful opposing views and that the term "acceptable minimum" is vague. As has been our practice for the past decade, we therefore designed conferences to bring together a multidisciplinary panel of health care professionals, philosophers, lawyers, administrators, and legislators to examine these issues. The conferences were structured not only to stimulate scholarly examination and debate but also to have practical value in clinical practice.

What Do We Owe People with Disabilities? Our 1993 conference stimulated controversy and confrontation from its inception. Our initial title—"What Do We Owe the Disabled?"—was attacked as demeaning, so the term "disabled" was changed to "people with disabilities." Objections were also raised to the word "owe" on the grounds that its connotation is somehow debasing. We explained to the objecting groups that, philosophically, a person who has a right to services or resources is owed those resources, and that because of the obligation someone has a responsibility to provide them. Then picketing was threatened in response to the title of Anita Silvers' paper, "Damaged Goods: Does Disability DisQUALify People from Just Health Care?" The threat was withdrawn only when it was explained that Professor Silvers is a disabled, wheelchair-using philosopher who intentionally had chosen a provocative title for her talk. This degree of sensitivity to language reflects the understandable vigilance of individuals who have been discounted, disregarded, and actively discriminated against by our social policies for too long.

As conference organizers in 1993 we were aware that, whatever the apparent power of the Americans with Disabilities Act and the legislation governing Medicare and Medicaid, our government was committed to reducing its expenditure on health care. We understood that there was only a thin line between limitations arising from ill health and limitations related to other disabilities. Indeed, a significant amount of the health care budget is spent on correcting for physical or mental limitation (for example: ambulette services, homemaker services, nursing homes). We, therefore, wished to examine the broader philosophic grounds for the Americans with Disabilities Act against the background of health care as a limited resource. As our experiences attest, this can be a difficult issue to raise, even by individuals who oppose today's

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threatened reductions in government spending for social programs.

Science, Alternative Care, and Third-Party Reimbursement. Once we raise the question of which care will be reimbursed by government and other third-party payers, we notice that many of the valued principles that govern medical practice can lead to conflicting social policy. Certainly we want traditional medical treatment to be evaluated by rigorous scientific standards. Indeed, a major portion of today's efforts to limit health care expenditures involves an assessment of the cost effectiveness of different traditional approaches to treatment. However, the information gained from cost effectiveness studies is used to justify restricting the care options that an individual can choose among. Embracing scientific methodology therefore clashes with our society's commitment to respect for individual choice.

Little of "alternative care" has ever passed the test of careful scientific study, and there is no reason to suspect that much would. We emphasize this point because the question before us cannot simply be resolved by a series of carefully designed clinical trials. At issue is whether scientific methodology will be the basis for medical decision-making or whether individuals will be allowed to choose among alternative theoretical models in making their health care decisions. Support for third-party reimbursement of alternative care does not simply hinge on the question of scientific evidence. Champions of alternative medicine at the national and state level argue that:

- many points of traditional, Western, scientific medical practice have not been subjected to rigorous evaluation

- different cultures have strong commitments to different theories of health and disease, and limiting access to alternative approaches to healing may disparage other people's beliefs
- many visits for health care are for minor self-limited or chronic problems that, once identified, may be addressed most effectively by using the patient's individual belief system
- the standards of scientific proof are elitist and arbitrary. This position seems related to the deprecatory view of science promulgated by creationists, who see science as merely one of several equally acceptable alternative points of view

When each individual pays for health care with personal money, our commitment to individual self-determination leaves individuals with a great deal of freedom to choose among the kinds of care that are available. This had been the reality of American health care until the last thirty years. Now, since most medical care is paid for by third parties, decisions about access to alternative care are being made through reimbursement decisions. As our social policy on access to health care is reshaped by legislation and changes in the private sector of health care delivery, the issue of the place of alternative medicine and medicine's commitments to science and personal choice will have to be adjudicated.

By presenting many of the papers of the 1993 and 1994 conferences on medical ethics in this issue of *The Mount Sinai Journal of Medicine*, we hope to contribute to the ongoing debate on government spending in support of people with disabilities and the debate on third-party reimbursement for alternative care.

Issues in Medical Ethics

1. What Do We Owe People with Disabilities?

Americans with Disabilities Act:

What the Act Mandates for Medicine

LORRAINE WHITE EGAN, J.D.

THE AMERICANS WITH DISABILITIES ACT (ADA) (1), which became law on July 26, 1990, has been heralded as the most significant piece of civil rights legislation since the Civil Rights Act of 1964. The ADA is designed to protect the approximately 43,000,000 Americans who have one or more physical or mental disabilities against discrimination, which, according to Congress, results "from stereotypic assumptions not truly indicative of the individual ability of such individuals to participate in, and contribute to, society" (2). In essence, the ADA requires that individuals who meet the essential eligibility requirements for a job or benefit not be excluded on the grounds of disability and that reasonable efforts (known as "reasonable accommodations") be made to enable individuals with disabilities to participate in such employment or benefits.

According to the findings of Congress set forth in the ADA, health services is one of the "critical areas" in which discrimination against individuals with disabilities exists (3). Since enactment, it has become increasingly apparent that the ADA will have a significant impact on the health care field. Current discussion has focused on three primary areas: health care reform, insurance coverage by employers, and access to treatment.

Overview of the Act. The precursor to the ADA was Title V of the Rehabilitation Act of 1973, which provides that "[n]o otherwise qualified individual with handicaps in the United

States . . . shall, solely by reason of her or his handicap, be excluded from the participation in, be denied the benefits of, or be subjected to discrimination under any program or activity receiving Federal financial assistance" (4). The ADA does not supplant the Rehabilitation Act of 1973, but instead extends the protections afforded to individuals with disabilities to both the public and private sectors.

The ADA is divided into five titles. Title I covers private sector employment. Title II applies to state and local governments and their instrumentalities (both as employers and as providers of services to the public), as well as transportation entities operated by state or local governments or their instrumentalities. Title III covers private sector public accommodations and private entities operating public transportation services. Title IV addresses telecommunication services. Finally, Title V addresses miscellaneous issues.

The ADA broadly defines "disability" with respect to an individual, in terms comparable to the definition of an "individual with a handicap" under the Rehabilitation Act of 1973, as follows:

- (A) a physical or mental impairment that substantially limits one or more of an individual's major life activities;
- (B) a record of such impairment; or
- (C) being regarded as having such an impairment (5).

Extent, duration, and impact are considered in determining whether an impairment "substantially limits one or more major life activities." Examples of major life activities include walking, speaking, breathing, performing manual tasks, seeing, hearing, learning, caring for oneself, and working.

According to regulations promulgated under the ADA (6), a physical or mental impairment is:

- [A] Any physiological disorder or condition, cosmetic disfigurement, or anatomical loss affecting one or more of the

Adapted from a presentation at the medical ethics conference "What Do We Owe People with Disabilities?" March 5, 1993, at The Mount Sinai Medical Center. From the Department of Legal Affairs, Mount Sinai Medical Center, New York City. Address reprint requests to the author, Vice President and Assistant to the President, Mount Sinai Medical Center, One Gustave L. Levy Place, Box 1074, New York, NY, 10029.

following bodily systems: neurological, musculoskeletal, special sense organs, respiratory (including speech organs), cardiovascular, reproductive, digestive, genito-urinary, hemic and lymphatic, skin, and endocrine; or [B] Any mental or psychological disorder, such as mental retardation, organic brain syndrome, emotional or mental illness, and specific learning disabilities (7).

Specifically excluded from protection under the ADA are homosexuality; bisexuality; transvestism; transsexualism; pedophilia; exhibitionism; voyeurism; gender identity disorders not resulting from physical impairments, or other sexual behavior disorders; compulsive gambling; kleptomania; pyromania; and psychoactive substance abuse disorders resulting from current illegal use of drugs (7).

For the most part, the ADA is enforced by the United States Attorney General and the Equal Employment Opportunity Commission (EEOC). Private rights of action also exist under the ADA for monetary damages, injunctive relief, attorneys' fees, and, under the employment provisions, punitive and compensatory damages.

The ADA and Health Care Reform

We are currently in the midst of a health care crisis in which costs escalate dramatically concurrent with a critical need to expand access to the vast number of Americans without any health care benefits. Serious issues have been raised regarding the impact of the ADA on reforms that attempt to "ration" health care by assigning priorities based on the expected outcome of treatment, such as the plan proposed by the State of Oregon.

The goal of the Oregon proposal was to extend basic health insurance coverage to the estimated 450,000 individuals in Oregon without insurance coverage by limiting certain benefits covered under its Medicaid program. The plan was intended to provide coverage to 120,000 additional people under Medicaid and would have required employers to provide insurance coverage for 300,000 workers lacking coverage.

The Oregon plan ranked 709 "condition/treatment pairs." Of these, the top 587 pairs (one was pregnancy/obstetrics care) were included in Medicaid coverage; the remaining 122 pairs (for example, non-Hodgkin's lymphoma/bone marrow transplant) were not covered. The ranking of these pairs was based on two primary factors: (a) an assessment of the expected benefit of the outcome for each pair and (b) public opinion on the importance and desirability of categories of health care services, obtained through public

hearings, community meetings, and a telephone survey.

To implement its plan, Oregon was required under federal Medicaid law to obtain certain waivers from the Department of Health and Human Services (HHS). On August 3, 1992, HHS denied Oregon's waiver on the grounds that its plan violated Title II of the ADA, which provides that "no qualified individual with a disability shall, by reason of such disability, be excluded from participation in or be denied the benefits of the services, programs, or activities of a public entity, or be subjected to discrimination by any such entity" (8).

In its "Analysis under the Americans with Disabilities Act ('ADA') of the Oregon Reform Demonstration," HHS concluded that the ranking of the condition/treatment pairs "was based in substantial part on the premise that the value of the life of a person with a disability is less than the value of the life of a person without a disability." First, HHS objected to Oregon's reliance on the results of the telephone survey, which was designed to determine public values on various states of impaired health or functioning using a scale in which 0 was death and 100 was good health. According to HHS, there were "substantial indications" that the survey "quantified stereotypic assumptions about persons with disabilities," in that persons without disabilities undervalued the quality of life of those with disabilities.

Second, HHS objected to the use of "certain community values, including 'quality of life' and 'ability to function,'" in the ranking process. According to HHS, "[t]hese two values place importance on 'restored' health and functional 'independence' and thus expressly value a person without a disability more highly than a person with a disability in the allocation of medical treatment." HHS concluded that "any methodology that would intentionally ration health care resources by associating quality of life considerations with disabilities does not comport with the mandate of the ADA." Instead, HHS advised Oregon to consider allocating medical resources by using "content neutral" factors, such as cost of medical procedures, length of hospital stays, prevention of death, and prevention of contagious diseases (9).

Finally, HHS challenged two rankings specifically linked to particular disabilities. The Oregon plan provided coverage for "nonalcoholic cirrhosis of the liver/liver transplant," but not for "alcoholic cirrhosis of the liver/liver transplant." According to HHS, this distinction was improper

because "the decision on coverage or no coverage is made entirely on the basis of a disabling condition (alcoholism)." HHS raised a similar concern about the differential treatment of premature babies based on birth weight, making additional reference to the Child Abuse Amendments of 1984 (which resulted from the "Baby Doe" conflict of the early 1980s).

HHS's ruling sparked considerable debate about the application of the ADA to health care reform proposals which use outcome-based, priority-setting criteria. The Oregon Department of Human Resources argued that the plan did not violate the ADA because ranking was neutral on its face, was not based on any discriminatory motive, and did not deny the disabled access to the standard health care services available to nondisabled individuals (10). Certain advocates for the disabled disagreed, arguing that the laudable goals of cost containment and expanded access cannot be accomplished simply by designating certain disabling conditions as unworthy of treatment.

Oregon resubmitted its waiver request to the Clinton administration, ranking 688 procedures and providing payment for 668. Quality of life considerations were removed as a factor in the ranking. The revised waiver request was granted by HHS in March 1993. The Oregon experience is likely to have a significant impact on the manner in which reform proposals attempt to allocate limited health care resources in the future.

The ADA and Employee Health Plans

Under a similar analysis, employee health plans are likely to be significantly affected by the ADA. Limitations on coverage for certain types of illnesses or treatments may give rise to liability under Title I of the ADA, which prohibits employers from discriminating against a "qualified individual with a disability" in regard to the "terms, conditions, and privileges of employment" (11).

The effect of the ADA on employee health plans is limited by a separate provision in the act pertaining to insurance, which states that the ADA should not be construed to prohibit or restrict employers from "establishing, sponsoring, observing or administering the terms of a bona fide benefit plan that are based on underwriting risks, classifying risks, or administering such risks that are based on or not inconsistent with State law (12). However, this section further provides that the insurance exceptions cannot be used as a "subterfuge to evade the purposes" of the act.

The application of the ADA to employee plans has been increasingly scrutinized as a result of the *H & H Music* case (13). In that case, an employee who had notified his employer that he had been diagnosed as having AIDS claimed that his employer violated the Employment Retirement Income Security Act of 1974 (ERISA) by subsequently reducing the lifetime benefits payable for AIDS-related claims from \$1 million to \$5,000 under its employee benefits plan. No similar limit was placed on coverage for any other catastrophic illness. The appeals court denied the employee's claim, holding that ERISA provides employers with broad discretion with respect to health care coverage and does not prohibit employers from discriminating in the creation, alteration, or termination of employee benefit plans. The Supreme Court declined to review the appeals court decision.

In his request to the Supreme Court that it deny certiorari in *H & H Music*, Solicitor General Kenneth Starr, apparently to the surprise of AIDS activists, suggested that although ERISA does not provide a remedy in such a case, the ADA may. Subsequently, the EEOC issued an Interim Enforcement Guidance on Application of ADA to Health Insurance. These guidelines make it clear that the EEOC will carefully scrutinize "disability-based health insurance plan distinctions" for compliance with the ADA. A number of lawsuits have since been filed by individuals claiming insurance discrimination under the ADA.

The debate over the effect of the ADA on employee health benefits is likely to continue for some time, with advocates for the disabled asserting that the ADA not only prohibits the kinds of limitations on benefits involved in the *H & H Music* case, but also other cost containment measures that have a greater impact on the disabled than on other employees. Employers are likely to respond that the insurance provisions of the ADA were specifically intended to protect against the wholesale reevaluation of existing insurance practices.

The ADA, Access, and Health Care Providers

Title III of the ADA prohibits discrimination against individuals with disabilities "in the full and equal enjoyment of the goods, services, facilities, privileges, advantages, or accommodations of any place of public accommodation by any person who owns . . . or operates a place of public accommodation" (14). Included in the definition of

"public accommodation" are hospitals and professional offices of health care providers (15). The ADA further provides that individuals with disabilities may not be denied "the opportunity to participate in or benefit from the goods, services, facilities, privileges, advantages, or accommodations of an entity" or be afforded treatment which is unequal, different, or separate (16). Title III does permit the exclusion of individuals when, as a result of a disability, they pose a "direct threat to the health and safety of others" (17).

These provisions of the ADA clearly prohibit discrimination by hospitals and other health care providers against individuals with disabilities (18). With respect to most hospitals, this prohibition is certainly not new; the Rehabilitation Act of 1973 prohibits discrimination against individuals with handicaps by entities receiving Federal financial assistance, which includes Medicaid and Medicare (19). Physicians arguably also are subject to the Rehabilitation Act to the extent that they accept Medicaid or Medicare. Moreover, many state and local antidiscrimination statutes contain similar prohibitions. For example, hospitals, as "public accommodations," are prohibited from discriminating against the disabled under both New York State and New York City antidiscrimination statutes. Physicians appear to be included in the New York City definition of "public accommodation" as well.

Areas of potential liability for hospitals and other health care providers include the imposition or application of "eligibility criteria that screen out or tend to screen out" individuals with disabilities, unless they "can be shown to be necessary for the provision of the . . . services . . . being offered" (20). For example, criteria for transplantation should not take into account disabilities that have no effect on the likelihood of success of the procedure.

Potential liability also exists where there is an unjustified refusal to treat a disabled individual. See *Glanz v. Vernick*, 756 F. Supp. 632 (D. Mass. 1991) (in a case under the Rehabilitation Act, the court held that a material issue of fact existed as to whether a patient who tested positive for HIV was "otherwise qualified" for elective ear surgery which his treating physician refused to perform). Similarly, inappropriate referrals may be challenged. For example, a dentist presumably could not refer an individual infected with HIV for routine dental care on the ground that he or she lacked the necessary knowledge or experience to treat the patient.

Conclusions

The ADA is currently having a strong impact in the health care arena. Enactment of the ADA has insured that the rights and needs of the disabled will be carefully considered on the national and local level in the ongoing debate about health care reform. At the same time, efforts by employers to control the cost of providing health care benefits by excluding certain medical conditions or treatments may be subject to challenge under the ADA. The impact of the ADA on hospitals and physicians is likely to be somewhat less dramatic in light of existing antidiscrimination statutes. Certainly, however, the ADA adds to the remedies available to the disabled to ensure that they receive necessary and appropriate medical care.

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1. Americans with Disabilities Act of 1990, Pub. L. No. 101-336 (codified at 42 U.S.C. §12101-12213, 47 U.S.C. §225, 611).
2. 42 U.S.C. §12101(a)(7).
3. 42 U.S.C. §12101(a)(3).
4. 29 U.S.C. §794(a).
5. 42 U.S.C. §12101(2).
6. 29 CFR Part 1630.
7. 42 U.S.C. §12211.
8. 42 U.S.C. §12132.
9. In support of its position, HHS cited *Alexander v. Choate*, 469 US 287 (1985), which held that a restriction on the number of Medicaid-covered inpatient hospital days was neutral on its face and not actionable as discrimination against the handicapped under the Rehabilitation Act of 1973.
10. Hercenberg JJ, Krasner W. Setting priorities. *Legal Times* Nov. 16, 1992, pl 20. The Oregon Department of Human Resources further argued that the telephone survey had no actual effect on the final rankings.
11. 42 U.S.C. §12112(a).
12. 42 U.S.C. §12201(c).
13. *McGann v. H & H Music Co.*, 946 F2d 401 (5th Cir 1991), *cert denied*, 113 S. Ct. 482 (1992).
14. 42 U.S.C. §12182(a).
15. 42 U.S.C. §12181(7)(F).
16. 42 U.S.C. §12182(b)(1)(A)(i)-(iii).
17. 42 U.S.C. §12182(b)(3).
18. See Cohen, Access to Medical Care for HIV-Infected Individuals under the Americans with Disabilities Act: A Duty to Treat, 18 Am J Law and Med 233 (1992); Note, The Americans with Disabilities Act: Magic Bullet or Band Aid for Patients and Health Care Workers Infected with the Human Immunodeficiency Virus? 57 Brooklyn L Rev 1277 (1992).
19. See *United States v. Baylor Univ Med Ctr*, 736 F2d 1039 (5th Cir 1984); *Glanz v. Vernick*, 756 F Supp 632 (D Mass 1991).
20. 42 U.S.C. §12182(b)(2)(A)(i).

What Does Anyone Owe Anyone?

PETER CAWS, PH.D.

... these double laws, of which we were speaking, are not exactly double, but they are in two parts, the law and the prelude of the law. The arbitrary command, which was compared to the commands of doctors, whom we described as of the meaner sort, was law pure and simple; and that which preceded, and was described by our friend here as being hortatory only, was, although in fact an exhortation, likewise analogous to the preamble of a discourse. For I imagine that all this language of conciliation, which the legislator has been uttering in the preface to the law, was intended to create good-will in the person whom he addressed, in order that, by reason of this good-will, he might more intelligently receive his command, that is to say, the law.

Plato, *Laws* 722e3–723a4 (Book IV)

MY ENGAGEMENT WITH the question of what we owe people with disabilities arises not from a medical or even a moral interest as such but from a long-standing concern with the nature of human society and its institutions—how these things are created and sustained, how people agree on design criteria or principles of inclusion, and so on. One dominant institutional aspect of society is the law, and a particular law, the Americans with Disabilities Act (ADA), has provided the stimulus for this conference. My epigraph, from Plato, suggests that what counts toward the effectiveness of the law is not just its text but also its context of discussion and persuasion. If philos-

ophy can be useful here it will be in this contextual way, helping people to “receive” the law more intelligently, as Plato puts it. (One note about the epigraph: when Plato says that an arbitrary command “was compared to the commands of doctors, whom we described as of the meaner sort,” he does not mean that doctors are people of a meaner sort but that only the meaner sort of doctor will give a command arbitrarily, that is, without prelude or explanation.)

The question posed in the title of the conference—“What Do We Owe People with Disabilities?”—is a complex question if there ever was one. Any answer to it has to negotiate agreement in at least three radically problematic areas. One of them—what is to be understood by “disabilities”—can for present purposes be simplified, at least provisionally, by accepting the definition of disability laid down in the ADA. Another—who “we” are—might be contextualized here and understood to mean the medical profession, although that would leave me out; I am not in a position to speak for the medical profession, and if I have anything to contribute it will have to be as a representative of some other collectivity—not philosophers (philosophers don’t form a collectivity and nobody speaks for them), but humankind in general, perhaps, or the body politic. I shall deal with this by assuming that all of us, whether doctors or philosophers or lawyers, are also members of what I shall call the “moral community,” and that the problem I have to address is what people in that community owe one another. Calling such a community “moral” certainly does not mean that it is a community of morally good persons, but rather defines a population to whose members moral considerations apply. How to define membership in the moral community, and what rights membership in it confers, are themselves disputed issues, about which I also have something to say.

Adapted from a presentation at the medical ethics conference “What Do We Owe People With Disabilities?” March 5, 1993, Mount Sinai Medical Center. From the Department of Philosophy, The George Washington University, Washington, DC. Address reprint requests to the author, University Prof. of Philosophy, Department of Philosophy, The George Washington University, Gelman Library, 2130 H Street, N.W., Room 714 U/V, Washington DC 20052.

What "Owing" Means

The third problematic area, and the one I shall concentrate on for the moment, is what it means to owe anything to anyone. All the dictionary definitions of "owe" say that to owe something is to be under an obligation (for example, obligation to pay a sum of money that is owed), but although this is no doubt true it is not that enlightening. Following the principle that a lot can be learned from the language, explore this cluster of terms for a moment. "Obligation" is being obliged, from *ob*, before (in the sense of "in front of" or "over against") and *ligare*, to bind—being bound to something in the light of some plain fact or condition (that's the force of *ob*, as in "obvious," something that's in the way, that one can't help stumbling over). "Owe," on the other hand, is equivalent to Latin *debo*, from which we get debit, debt, and so on; the past form of the Germanic root verb gives "ought," the past participle gives "own," both of which have become English verbs in their own right. So there is absolutely no etymologic connection between "oblige" and "owe," but there is a direct connection between "owe" on the one hand and "ought" and "own" on the other, which is suggestive in the present context. People with disabilities ought to have lives of their own, with all that those terms imply—on that we might all agree. But does that mean that any particular persons owe them anything, are under any obligation to them? The question is, just how indebtedness binds, and to what or to whom.

If I think of my own indebtednesses and their grounds I come up with four main categories, personal, cultural, moral, and legal.

Personal Indebtedness. I am personally indebted to friends, relatives, and loved ones, and I owe them gratitude, affection, and support. This does not feel in the least burdensome; on the contrary, the discharge of these obligations is part of what makes me what I humanly am, part of my enjoyment of that condition.

Cultural Indebtedness. However, to take a related example close to home, I have an obligation also to my infant daughter, to shelter and nurture her, though I could not be said to be indebted to her in the same sort of way. Here there is a transition to cultural indebtedness, since I owe this particular obligation (I use this intensifying device deliberately) to the traditions of parenthood and family life with which I grew up. Related traditions have inculcated other obligations as well. I am indebted to generations of teachers, writers, composers, thinkers, research-

ers, engineers—and to some warriors and statesmen and even administrators—for the practical and intellectual conditions of my life, and feel obliged to protect and strengthen, as far as in me lies, the structures of learning and the social institutions I have inherited from them.

Moral Indebtedness. Whereas many of these social and cultural obligations were bred into me so that they are quasi-automatic—like feeling obliged to walk on the outside if my companion is a woman, to open doors, to offer seats in buses, though I'm learning to control these reactions when it is obvious they are not desired—I have also thought a lot about them, and in general about the question of what I ought to do. And these cogitations have brought with them another set of obligations, those I impose on myself as an autonomous moral agent, among other things as conditions of self-respect, perhaps even of self-identity. It is not so clear here to whom the indebtedness is incurred. In a way it is to humankind, in a way to myself: I owe it to myself to behave in accordance with my own standards, on pain of self-alienation. But then I find that I also owe it to any other moral agent to care about the conditions of his or her action as such, and this is a line I develop below. It is here I think that we shall find the best answers to the question of what we owe people with disabilities.

Legal Indebtedness. Finally, some indebtednesses arise from my formal relations to others and to the institutions we mutually sustain, among which I distinguish between contractual and statutory cases. Two banal examples that can stand for all the rest: first, I owe money to the bank that holds the mortgage on my house, because of a specific contract entered into when I bought it; second, I shall shortly, I fear, owe money also to the Internal Revenue Service, not because I have any contract with them but because the law tells me I must pay, and how much. (A contract theory of government would trace such statutory obligations to contractual ones at a deeper level: there is an implicit contract between us and our fellow-citizens to obey laws voted by the legislators we elected, or in my case, strictly speaking, an implicit contract with my hosts to obey laws voted by legislators they elected, as a condition of enjoying my status as an alien or *metoikos* in their polity.)

Moral Indebtedness and Membership in the Moral Community

Up to this point I have not been feeling any particular obligation to people with disabilities. I

could rest my case on legal indebtedness and say that what we owe them is no longer a problem because it is spelled out in the ADA, but if it were that simple we would not be having this discussion. Again, cultural indebtedness involves certain ingrained attitudes, for example of compassion to those less fortunate than oneself; but culturally derived obligations inculcated as reflexes, probably at the level of the unconscious, cannot be relied on generally, especially at a time when transmitted cultures are in crisis, if not in full retreat. Also this route smacks of charity, which is not what is wanted.

What kind of argument might be constructed on moral indebtedness that would rely neither on the force of law nor on the hazards of a variable and idiosyncratic cultural transmission?

A Self-Defining Moral Community. I begin with the idea of a self-defining moral community, self-defining because I want the conditions of this discussion to be as general as possible and its presuppositions as few as possible, so that no recourse can be had to any a priori or transcendent authority in setting terms of membership. This self-definition has in fact evolved—the moral community used notoriously to exclude slaves and women, for example, but with time, and in principle at least, slavery has been abolished and women fully included. The exercise of self-definition continues, as in the case of fetuses—whether, and at what age, they should be counted as members. As this case shows, there are distinctions among kinds of membership, some for example being passive and some active; the fetus certainly does not owe us anything, but if and when it comes to belong to the moral community we owe it something. Similar considerations might apply to animals. By and large such considerations will not, I think, apply to people with disabilities, who would wish and deserve to be active members—but there may be hard cases, especially in view of the inclusion of mental impairments in the definition of disabilities.

Membership in the moral community has something in common with participation in society as conceived by Aristotle: if you're human, you belong; anyone who can't relate to others at all, or is totally self-sufficient and thus doesn't need to, "must be either a beast or a god: he is no part of a state" (in his *Politics*, Book I, ch. 2). So one criterion of membership is the criterion of humanity, a point I will not pursue into the thorny territory of animal rights, though some domestic animals seem unquestionably to be honorary members. Because of its self-defining and self-legislating character, the moral community

is a place of perpetual argument—about its own limits, about better and worse institutional forms, and so on. (A general observation, relevant to all discussions of value: it is possible to know the better even if one does not know either the good or the best—insisting on them is what is practically wrong with many moral theories. Children learn the dimensions of value through experiences of preference, which suggests that the comparative is more basic—empirically if not logically—than the positive and the superlative. Also we often have the experience of agreeing that of two examples of a kind, say paintings, one is better than the other, without being able to agree on or even specify what constitutes "the good" in painting or on what the best painting might be like.)

The pattern of argument in moral theory is: if such and such moral principles are adopted and acted upon, such and such a world will result; is this a world we want, is it a better world than would result from alternative principles? I stress "and acted upon" because adopting principles is one thing, putting them into practice often quite another. Putting the principles of the community into practice is something that devolves separately on every member. Few people have said this more trenchantly than William Blake:

He who would do good to another, must do it
in Minute Particulars

General Good is the plea of the scoundrel
hypocrite & flatterer.

Privileges of Membership: Equality in Freedom. Membership in the moral community has privileges, the chief of which is equality with all the other members. There has been a lot of argument about what factors are to be equalized in order to achieve this; my own candidate is, simply, freedom. (My whole argument is too long to review here, but it was set out in 1967 in my book *Science and the Theory of Value*, a new version of which is about to be published under the title *Ethics from Experience* [1].) The form equality takes can be summed up in a principle that I call the principle of indifference: there is no argument capable of showing that the freedom of any one individual in the moral community should be privileged over the freedom of any other individual in that community.

Inhibitors of Freedom. However, freedom is a complex matter; for me an act is wholly free if and only if the agent:

- is unrestrained and unconstrained
- understands and intends the act (and understands the intention)

- has at his or her disposal adequate resources of
 - bodily strength, dexterity, etc.
 - energy and material, including tools, machines, etc.
 - information about the state of affairs (the context of the act)
 - knowledge of relevant natural and social laws (that is, the probable consequences of the act)

In other words, people who are actively prevented by others from doing what they want (or coerced by them into doing what they don't want) are not the only ones who are not free: a lack of motivation, a lack of self-knowledge, a lack of strength, a lack of resources, a lack of information, a lack of scientific knowledge can each be an equally effective inhibitor of freedom in the full sense. As I put it in *Ethics from Experience*, "Slaves are not free, and most people are in agreement about that. What is not always so clear is that poor are not free either, and even the rich and powerful are not free if they are ignorant." I would now add this: people with uncompensated disabilities also cannot be free in the full sense.

But freedom is just what the moral community as I understand it is committed to equalizing. It follows from the foregoing definition, along with the principle of indifference and the rule of double negation (for details of the argument I must send you back to *Ethics from Experience*, ch. 11), that I can contribute to the unfreedom of my fellows both positively and negatively—positively if I restrain or constrain or discourage or maim or deprive or mislead or deceive them, and also negatively if I fail to liberate or protect or inspire or heal or supply or inform or educate them. My contributions are subject to obvious pragmatic cutoffs having to do with my own abilities and resources, and subject also to the proviso that these things may be done collaboratively—Sartre to the contrary notwithstanding, I needn't carry the whole weight of the world on my shoulders. I am also morally implicated if I subscribe without protest to a social or political system that impairs their freedom either positively or negatively.

What We Owe: Equal Freedom of Action. The upshot of this line of argument is that if we take the idea of the moral community seriously, and if people with disabilities are full members of it, then we have to design that community and distribute its resources in such a way as to bring their freedom of action into line with ours. That is one of the things we would seem to owe them.

Putting Equal Freedom into Practice

As a matter of principle I have no doubt that this aim is right, but of course it is just here that the problem of putting principles into practice rears its head; general good has spoken, and now we have to get down to minute particulars if the charge of hypocrisy is to be avoided. (Only a few philosophers have so far been willing to grapple with this issue in the specific context of people with disabilities; two courageous and useful attempts worth citing are those of John McDermott [2] and Eugenie Gatens-Robinson [3].)

Pragmatic Cutoffs and Widespread Commitment. Here there are a number of lines of reflection that I will only sketch, given the confines of this paper. The idea of a pragmatic cutoff governing the efforts of members of the moral community shows up in the ADA in expressions like "undue burden" or "readily achievable," which can be construed as meaning that, for a while at least, the mandates in the act often won't happen. Those mandates could happen if the decision were made to fund the mandated changes, but the unspoken assumption is that that would cost too much, and indeed perhaps it would—though "too much" is obviously relative to the degree of individuals' commitment to a just order of things. (Legislation without a corresponding appropriation would certainly have seemed to Blake the work of the "scoundrel hypocrite & flatterer.")

A deeper question is whether enough individuals are really committed to the realization of equalizing freedom in moral community. Given the frequency with which healthy but impatient people park in handicapped parking spaces, the answer to this question would seem clearly to be no. This, then, is a job for education, not just about people with disabilities but about the very concept of a moral community, one's place in it, and one's obligations to its other members. What people owe people is to recognize them as moral equals, the protection of whose freedom is a communal responsibility.

The number of people committed to this recognition bears a direct relation to the question of the pragmatic cutoff: the more people agree that something ought to be done—about facilities for the disabled, for example—the higher the cutoff can be, since a modest contribution on my part, joined to everyone else's, will easily do the trick as long as the disabled are not statistically dominant. So another thing we owe the disabled is the enlightenment of those who have not accepted their full status as members of the community—not just penalizing the offenders after they have

offended, but drawing their (and everyone's) attention to their own moral situation and the obligations this imposes. Such instruction cannot be forced so as to compromise in turn the freedom of previously insensitive persons, but there are ways of getting the message across in such a way that if it is not received, the responsibility rests squarely on those to whom it is addressed. As T. S. Eliot says in "Gerontion," "After such knowledge, what forgiveness?"

At this point, however, broader questions intrude. Why especially the disabled? and why only Americans? The considerations that work for disabilities work also for health care generally, and for income support; the principle of indifference won't allow us to privilege the freedom of disabled people over those disadvantaged in other ways, and if honestly applied it won't allow us to privilege the freedom of Americans either. What the world needs is a *People with Disabilities Act*. But it also needs a *Poor People Act*, and a *People Who Went to Bad Schools and Spent Too Much Time Watching Television Act*, and a *Credulous People Who Believed Demagogues and Televangelists Act*. For I do believe that credulity ranks with mental retardation when it comes to the kind of disability that cripples social betterment. But that again is another story.

Society and Community. The Americans with Disabilities Act is certainly a step in the right direction, and the political energy that went into its passage can only be applauded. The act operates along the societal rather than the communal axis, bearing in mind Ferdinand Tönnies' distinction between *Gesellschaft* and *Gemeinschaft* (from his 1888 book with that title). Society characteristically tries to solve by legislation what community would solve by education—in our specific case the recognition of the abilities of people with disabilities. In considering the epigraph from Plato I begin this essay with, one might think of the law as *gesellschaftlich* and the prelude to the law as *gemeinschaftlich*. Perhaps it is stretching things to assimilate society to socialism and community to communitarianism, but when I read in the ADA Handbook (4):

Enactment of the ADA reflects deeply held American ideals which treasure the contributions which individuals can make when free from arbitrary, unjust, or outmoded social attitudes and practices that prevent the realization of their

potential. The ADA reflects a recognition that the surest path to America's continued vitality, strength and vibrancy is through the full realization of the contributions of all its citizens

there echoes in my head an older motto: "From each according to his ability, to each according to his needs!" (5).

We no doubt need both types of institutions—both the societal and the communal—but for me the question of what we owe one another is far more interesting in the community context. People owe other people, including people with disabilities, the mutual aid and respect that goes with being a member of the moral community, including the grateful acceptance of whatever contribution to that community the other person, however disabled, is in fact able to make.

I remember being told by the French poet René Char about a village that practiced this kind of community spirit. One of the villagers was disabled, but he had a useful job, like everyone else, and one in which he took some pride: the job of clacking a couple of pieces of wood together in the evening to silence the local frogs, so the rest of the village could go to sleep. The bottom line here, I think, is ceasing to notice the disabilities people have, ceasing at any rate to make any kind of fuss over them. Nobody is just generally "able"; why should anyone be considered essentially "disabled"? What we can do we can do, with mutual satisfaction. That will include in the end—and I will believe the problem solved when it happens—laughing together as well as working together. In the matter of wounded sensitivities we have a long way to go before we can put ethnic and social and situational tensions behind us. Having discussions about it should be of some help.

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Sustainable Justice and Resources in Support of the Disabled

ANDREW JAMETON, PH.D.

Only help her to know—help make it so there is cause for her to know—that she is more than this dress on the ironing board, helpless before the iron.

—Tillie Olsen, "I Stand Here Ironing" (1)

IN NOVEMBER 1992, the Union of Concerned Scientists published "Warning to Humanity," a brief statement (2) signed by about 1,500 scientists around the world. The statement warned that "human beings and the natural world are on a collision course," and that we must greatly reduce our per capita use of natural resources if "vast human misery is to be avoided" and if "our global home on this planet is not to be irretrievably mutilated." The statement called attention to the exponentially worsening condition of the biosphere and the rapidly burgeoning damage to the atmosphere, fresh water, oceans, soil, forests, and living species. The statement urged rapid economic and social changes, within one or a few decades, including "moving away from fossil fuels, more efficient resource management, stabilizing population, reducing and eventually eliminating poverty, and ensuring sexual equality."

This statement is of course just one, albeit concise and authoritative, of many similar warnings about the fate of humankind and the biosphere in the next fifty to one hundred years,

warnings which display an almost unremitting pessimism that is difficult to face. Charles Mann has labelled these prophets Cassandras and contrasts them with Pollyannas, who see human population as conceivably reaching 30 billion without serious permanent harm to the environment. Pollyannas accuse Cassandras of insufficiently heeding potential technological development and market-driven change, and underline the uncertainty of many environmental prognostications. To me, however, the work of the Cassandras seems careful, humane, and comprehensive, while the Pollyanna literature appears to suffer from narrowness, vested interest, and a poor understanding of capital and entropy limitations on potential gains from new technologies.

Although the Cassandras sound pessimistic, they are not completely so. Most of them believe that the collapse of human welfare and massive extinction of species can be avoided if strong and prompt action is taken. They thus bring us the good news that change toward sustainable human politics, economics, and ethics might still be possible. Indeed, they are more optimistic than the Pollyannas, who tend to regard current economic and political arrangements as inevitable and unchangeable.

Among the most important changes for which Cassandras call is a limitation on resource use and the elimination of poverty. Clearly, both wealth and poverty are major contributors to environmental degradation. On one hand, wealthy consumerist societies process incredible quantities of fuel, electricity, metals, and agricultural products and spew forth correspondingly immense quantities of carbon dioxide, waste, and toxic pollutants (3). They also create poverty by sequestering resources throughout the world that could be used more broadly and equitably for the

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world's growing population. Poverty, meanwhile, compels people to overuse marginal lands, to plan only for the short term, and to forgo conservation practices requiring technology and capital. The world's rich and poor together speed the destruction of the biosphere.

In short, the Cassandras are recommending that the world move rapidly toward greater equality in the distribution of resources. I think we need to take them seriously. Equality has long been an ethical ideal; it is now becoming a necessity for survival into the twenty-second century. And I think that taking equality in resource use seriously has implications for how we should approach problems of health care allocation. Indeed, taking this global and long-term view into account, two nearly universal features of the discussion of just health care allocation need to change: We need to set health care reform in the context of larger economic changes than we have so far, and we need to discuss justice in terms more concrete than dollars.

The Larger Framework of Equality

Justice in health care is almost always discussed within an underlying framework that accepts the U.S. system of consumerism, poverty, and unrestrained accumulation of wealth. If the Cassandras are correct, this framework must change. Meadows et al., in their excellent 1992 reworking of the 20-year-old Club of Rome report, argue that a sustainable world is possible only if the world's average industrial output does not exceed roughly \$350 per capita (4). This is a small fraction of the current United States per capita industrial output. If we must also achieve relative equality and an overall low level of industrial output, first-world countries will need to scale their living expectations way down—we must move to an economy in which consumerism, achievement of wealth, and resource use are limited.

Unfortunately, many people draw different conclusions from observing our developing global circumstances. When I present my talk about biospherical bioethics to medical students, I hear reactions from some students that I label "casual Malthusianism." Students say, for example, that the AIDS endemic is good news, because it will help to reduce the world's population. Or, since many of them were biology majors as undergraduates, I hear Darwinian rumblings about the survival of the fittest. Or, they say, the third world has a population problem, but not the first world.

I am disturbed by these reactions partly because my students seem not to realize that AIDS is not limiting the world's population, that populations are threatened, not individuals, and that the impact of population growth is being felt worldwide.

I am also disturbed by these casual remarks partly because I also hear in them a callousness toward human life at a distance that does not speak well for members of a profession purportedly dedicated to service. I feel disturbed, even though I realize that this attitude is not confined to my students. I grew up in the Midwest—a world in which one unfortunate consequence of individualist philosophy is that respect for human life overemphasizes the close and nameable, but does not extend to people in general. We see this philosophy displayed in many ways. We see it in the two centuries of United States neglect of public health in favor of an overdeveloped tertiary care system. We see it in our aggressive national struggles to dominate petroleum, metal, and agricultural sources the world round. We see it in the philosophical questions my colleagues address. Philosophers puzzle, for example, over whether it is morally acceptable to switch a streetcar onto a track that will kill one person in order to save five people on the other track—yet we actually live in a world in which our health policies allow five to die to save one, and this philosophical problem is rarely addressed. This callousness toward life at a distance we especially see in the movies. We regret the overt violence in them and on TV, but we often fail to notice the body count in the background, the many deaths sometimes scripted into the background to move the plot ahead. The most obscene in recent years was the supposedly light comedy "Joe and the Volcano," in which to bring two young lovers (Tom Hanks and Michelle Pfeifer) together, an entire island and the tribe on it was blasted to smithereens. I feel that I live in a culture that loves life in the foreground and death in the background.

This is one way to approach the biosphere crisis. In a world of increasing scarcity and greater population, we can continue to build a culture that saves a few at the cost of many, in which everyone must struggle for wealth in order to avoid marginality, and in which we emphasize deservingness and distinctions among people in order to justify hundredfold disparities in the control and use of resources. Plato recommended a ratio between rich and poor of just four to one. But in 1988, to take only one example, "Michael Milken . . . made 1400 times more than the Teacher of the Year" (5). I think such disparities

have been the clear choice in the United States and many other places. I think many of us would and do choose to allow many to die if we think it will enrich us further, and as long as the deaths are in the background, and at a distance.

But, as the Cassandras are arguing, this "island" mentality purports an ultimately suicidal course. Building great wealth for some at the expense of others portends environmental and human ruin in the next hundred years. Instead, we should choose the course of greatly increased equality of resource use. This would have healthy consequences both for the world at large and for the provision of resources for the disabled.

Politics on behalf of the vulnerable often involves choices on whose needs to champion. In the last decades, we have heard from older adults, children, women, people living with AIDS, the poor, the uninsured, the disabled—all groups with marginalized members. Sometimes we call attention to common needs and interests among groups; at other times we hear such groups competing with each other for primacy in access to scarce resources. And the numbers of the vulnerable can be greatly extended; much of the world's population is vulnerable because of unstable food supplies, unclean water, and the lack of stable employment. Indeed, looking ahead into the next century, all human groups are vulnerable; in this century many plant and animal species have become extinct.

Justice and Concrete Resources

The truth is that the needs of the disabled for concrete global resource—fuel, metal, heat, food, plastic—are not much different from others' needs, except for a few who are severely disabled. The needs of individuals for resources are set much more by the surrounding technologies that determine methods of food production, public transportation, power generation, medical technology, and so on than by particular individual needs. Moreover, great wealth and widespread consumerism produce much greater inequalities in resource use than does providing for the disabled.

Unfortunately, ethicists almost always discuss health care allocation in terms of dollars instead of concrete resources, such as employment, bricks, plastic, chemicals, fuel, time. As I used to point out jokingly to my students, but now note more seriously, healthy babies are potentially much more costly to the earth than sick ones, because a healthy baby in the United States will be more likely than a sick one to grow up to make

lots of money, eat meat, drive cars, drink soda, read books and newspapers, and ride in airplanes. The average U.S. automobile exhausts roughly its own weight in carbon into the atmosphere each year (6). That the automobile is private property will do nothing to reduce that output. We might thus picture the temporarily abled out racing in the streets as really disabled—as driving expensive steel, glass, and aluminum prostheses, necessitated by our abnormal inability to travel more than five miles per hour on legs. My car represents a major social investment of the world's resources, surely more than a wheelchair or a special bed. Indeed, we tend generally to maintain altogether too much tolerance for the uncontrolled use of privately held resources, while the global biosphere crisis requires policies that encourage more efficient personal resource use for everyone.

Moreover, in thinking about resources concretely, it is important to distinguish the costs of human labor from the costs arising from the use of natural resources (7). Many of the disabled simply need human assistance, and many people in the world are in need of work. Unfortunately, the current trend of U.S. business, including health care institutions, is to cope with dollar shortages by laying off employees and reducing staff. Although it does not look good on the budget and reduces measures of productivity, hiring more attendants and aides creates human benefits, not resource costs.

Indeed, although discussing dollars in allocation has an important place, using dollars as the single surrogate for resources is seriously defective. In addition to inaccurately representing actual resource use, dollar costs in the United States are also always dollar benefits. Every spender is matched by an earner. This means that every effort to cut costs is also matched somewhere by income loss to someone or other. We don't know what the actual resource impact of dollars saved is unless we know impact on both the spender and the recipient in resource use and consumption. The disabled appear resource-costly largely because of the monetary budgets they are on and because we view the dollar amounts involved in their care as costs to society, when they could just as easily be regarded as benefits to society.

Expending Public Resources. What then should we say to questions of how much of our public resources to expend to make our public places accessible to the disabled? I think that we need to make a basic choice about how we are going to approach the coming biosphere collision.

I think we should choose strong principles of equality of resource use, and thus we should wherever possible make public spaces and medical care equally accessible to all. In general, features friendly to the most common forms of disability should be built into the architecture and landscaping of any new construction; they should not be regarded as add-ons. Likewise, the basic package of medical care should include ample assistance to the disabled. Rationing and triage with regard to health problems should take place largely prior to and at birth, but once past that point, people should receive even-handed support and assistance throughout life, whatever misfortunes they incur and whatever age they may reach.

Nonetheless, I think it is possible to expend excessively to help a few individuals. Indeed, I think there is something of a collusion between purveyors of expensive medicine who stand to profit, on one side, and disability rights advocates unwilling to draw the line on resource use on the extremely and desperately disabled lest it threaten the much less disabled. But the problem here does not lie with the advocates or with the purveyors, but with an economy that exaggerates services at the expensive end, as in intensive care units, and neglects long-term, labor-intensive services. Right now, our large and excessive private system establishes standards of care that involve extremely high rates of resource use. Those who lack access then argue that they are unfairly excluded from the excess. Everyone should be entitled to access to excess. Right. But if we come to terms with a world of limited resource in health care and in our lives in general, including everyone within the purview of care will not be so costly.

Care will be much less costly in two respects. First, the primary investment in health care will be in public health and the services that are most effective and useful throughout life; to care for the disabled, we will not need to support a large investment in exotic life-saving therapies. Second, those being rewarded for the provision of health care will receive the same modest incomes and have the same modest needs as the vast majority of people on earth; thus, the dollar and consumer costs of providing health care will be substantially less.

My response to one of the more troubling questions of resource use is then this: We can justifiably limit use of health care resources for those suffering multiple and severe disabilities at birth when those disabilities can be only slightly ameliorated by great investment in technology—

but the justification only holds while we also stop allowing individuals to expend extraordinary amounts on themselves in two-car families, massive houses, and huge collections of consumer items.

Conclusions

I am convinced that our global predicament can and must color every discussion involving resource use. Moreover, I am sure that we need to think more in terms of the use of concrete resources and less in terms of dollars. Dollars should serve our needs and welfare, not the other way about. An awareness of the crisis in the biosphere can and should lead us to a stronger sense of equality and unity among humans, instead of to reflexes of hoarding, jealousy, and mistrust. This greater sensitivity to the vulnerability of human and nonhuman populations as a whole offers a stronger realization of unity with the disabled, and of the disabled with the temporarily abled. The movement to health care reform should be part of larger reforms in the economic management of transportation, housing, food, and other necessities. As Schumacher pointed out in the opening of his book *Small Is Beautiful*, we have not yet solved the problem of production (8). And as the Union of Concerned Scientists warns, we have a little time, but just a little, left to do so.

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7. I do not distinguish in these discussions between renewable and nonrenewable resources, nor between recyclable and nonrecyclable materials. Although recycling will help, the remanufacture and reuse of materials costs energy, equipment, and materials. Recycling will not be enough to permit consumerism to proceed unabated; instead nonuse and reuse have to precede and surpass recycling. The production of renewable resources also requires land, energy, and materials, and so these are also ultimately limited as well.
8. Schumacher EF. Small is beautiful: economics as if people mattered. New York: Harper & Row, 1989, 14.

Duties and Decency

PETER C. WILLIAMS, J.D., PH.D.

Abstract

Though we should help improve the lives of those with disabilities, it is not because we owe them help. The paper begins with a discussion of some features of disabilities: they are defining, ubiquitous, mutable, context dependent, and normative. The moral meaning of "owing" is analyzed and sources of moral duties set out and related to the moral claims of the disabled. Finally the paper suggests that decency—a minimal concern for the welfare of those whose lot we can improve—is a richer way to explain the moral propriety of helping the handicapped.

A THOUGHTFUL ANSWER to any question begins with attention to determining precisely what is being asked. The conference query, "What do we owe people with disabilities?" prompted two sets of initial reflection: first, what are we talking about when we discuss people-with-disabilities? Second, and more important, is "owing" the best way to think about our moral relations with the disabled?

Some Preliminary Thoughts about People with Disabilities

Disabilities Are Defining. The first striking feature of disabilities is that, though they appear to be attributes—"people with disabilities"—they are better thought of as defining characteristics. We don't simply have disabilities; rather, disabilities define who we are. Though people sometimes acquire and eliminate them, disabilities are not attached to us like articles of clothing or living in us like viruses. Disabilities determine the kind of people we are. They are essential to how we view ourselves, how other people view us, and the role

or place we have in our shared community. Recognition that disabilities are defining is important to our discussion because the kind and extent of our moral responsibility toward others turns on it. Actions that reflect on or respond to one's essential self are particularly important morally. One reason race and gender play such a central role in discussions of social justice is that these two features are central to who we are. We don't have a gender; we are one. Disability, too, as a defining feature of our self, has a crucial influence in defining our social responsibilities toward people who are disabled.

Disabilities Are Ubiquitous. The second feature of disability worthy of special note at the outset is their ubiquity. We all had disabilities as children; we all have them now, and we'll certainly have more of them as we get older. The answer to the question what we owe the disabled affects us all. The ubiquity of disability makes easier the application of Kant's notion of universalizability. Our stance toward people with disability is one that will apply toward us all.

Disabilities Are Mutable. In addition to their ubiquity, disabilities are mutable. They are more and less; they are partial and complete; they come and go. The whole issue of what constitutes a disability and one's obligatory response to it turns on these variables. Whatever our answer to the question of our duty toward the disabled, it will vary proportionately with the severity, comprehensiveness, and temporality of the handicap.

Adapted from the author's presentation at the medical ethics conference "What Do We Owe People with Disabilities?" March 5, 1993, Mount Sinai Medical Center. From the Division of Medicine in Society, Health Sciences Center, Stony Brook, NY. Address reprint requests to the author at the Division of Medicine in Society, Health Sciences Center, 3L-086, Stony Brook, NY 11794-8036.

Disabilities Are Context Dependent. Fourth, the way in which disabilities vary marks another of their crucial features: handicaps are context dependent. The degree to which we are disabled depends on where we are and what we are trying to accomplish. My inability to run a four-minute mile—an incapacity I have had my entire life—does not disqualify me or keep me from doing virtually anything I wish to do or anything I need to do. The context dependency of disabilities has two important implications. First, it gives us a way to judge the severity of handicaps. What makes some disabilities more serious than others is the degree to which they prevent us from accomplishing the primary features of a minimally good life—surviving, producing, mating, collaborating, navigating, loving, and so on. An intelligent discussion of our duties toward the handicapped would require attention to the capacities needed to live a minimally good life.

Another lesson to be learned from the recognition that disabilities are context dependent is that one can overcome a handicap by altering the context, not the person. This is especially important when we recall the first feature discussed above, that disabilities define who we are. If we can enable the disabled by altering the world and not the person, we will have made a morally significant intervention without changing the individual character of the person.

Disabilities Are Normative. Finally, what we consider a handicap or disability is obviously normative, in both the evaluative and descriptive sense. Being handicapped is considered bad. In a culture where “doing and accomplishing” are valued, being disabled is dis-valued. Moreover, handicapping conditions are outside the “normal.” They are atypical. None of us can, unassisted, see infrared light, though being able to do so would be an advantage in many situations. We do not consider this lack of capacity a disability because we all share it and do not expect to have the ability.

Each of these features of disabilities—they are defining, ubiquitous, mutable, context dependent, and normative—has implications for the question of our responsibility toward the disabled. Nonetheless it is a second aspect of the question—is “owing” the best way to think about our moral relations with the disabled?—that I found more challenging and helpful.

Some Preliminary Thoughts About Owing

Answering a question about what we owe people with disabilities really raises two issues:

first, do we owe anything to the disabled? and second, if yes, what do we owe them? The first of these questions raises the threshold philosophic question about moral theory, and that is the focus of my remarks. I suggest that the language of debt, of “owing,” is the wrong way to think about our moral responsibilities toward the disabled. In doing so I hope to draw a sharp distinction between two related, but importantly different, questions:

Ought we to accord the disabled
special treatment?

vs.

Do we owe the disabled special treatment?

Rights, Owing, and Moral Demands. Separating these two questions, as I hope to do, runs counter to our contemporary political discourse. For the last 30 years public debate about civic morality has been skewed toward talk of rights and their correlative duties, on what we owe each other. People’s claims on each other individually and on the community as a whole have been cast in terms of rights. Minorities, women, children, lesbians and gays, the ill, workers, and a plethora of other groups have based their normative claims for attention or assistance not on their needs but on what they assert they are owed by society. An example well known to physicians is the debate about how to treat the institutionalized mentally ill. The conflict was cast in the media as well as the courts not in terms of the good that better medical care would bring to those suffering from mental illness, but as a claim of a right to medical treatment, that the mentally ill were owed therapy by virtue of their illness. The issue was ultimately argued in terms of requital, that is, treatment was owed not because someone was ill but because they were incarcerated. Nonetheless the early debates spoke more clearly of the right to be treated for illness *per se*.

Why has our discourse turned from concern with welfare to talk of rights? Part of the reason is our collective view that rights are a special sort of thing. They have what I call a demand quality to them. When somebody claims a right to something, they are not just asking for it or saying that their receipt of that thing would be morally proper. They are morally demanding that they receive it; that it is owed them; that others have a duty to provide it. When you say you have a right to something, you are asserting that if you get it you don’t have to say thank you. You deserve it in some sense, and if you don’t get it you’re not just disappointed, you’re indignant. Our question about owing the disabled something requires that

we think about what that particular kind of moral claim entails. We are being asked whether our failure to afford the handicapped special treatment would support indignation, and whether it would be inappropriate for the handicapped to be grateful when they receive it.

Decency and Kindness. In the end I want to make a case for using a different kind of language, to think about our relationships with the handicapped in terms of decency and kindness, not rights, duties, and debt. The starting place must be an understanding of what it means to "owe" something.

Philosophers—at least those in the Anglo-American tradition—look to usage to determine the meanings of concepts. A common way to begin is to look at the etymology of a word. The origin of the word "owe" is the Old English word *āgen*, which means "to have or possess." The word "own" is also derived from *āgen*. The sense of possession and obligation involved in these terms is unmistakable. Debts are owed; duties are owed. One can demand what they are owed.

Our universe of morally good actions is broader than things owed or things it is morally appropriate to demand. I am briefly going to describe that richer universe and then ask in what part of that universe the claims of the disabled belong.

Morally right actions are typically classified as actions which are supererogatory, actions which are obligatory (duties), and actions which, though neither heroic nor obligatory, we ought to do. All of these actions are morally laudatory.

Acts of supererogation are those above and beyond the call of duty. This is the domain of heroes and saints. Super-Samaritans do morally good things that they are not morally required, that they don't have a moral duty, to do. They do them to help. They do them to do good. We all know people who perform acts of supererogation. Feeding children in Somalia serves as an example. Adopting disabled children is an act of love and beyond anyone's claim of duty. Donating an organ, bone marrow, or blood to a stranger is supererogatory. The beneficiaries of these acts of moral largesse are not "owed" these benefits. They have no moral claim to them. This is a category of morally good action that is other than owed, other than duty, other than debt.

As noted above, "owings"—obligations, duties, and debts—seem to be the most popular category of morality in our public discourse. In the law, repaying debts and keeping promises are all obligatory. Appropriate behavior is owed others. Obligations exist in the private sphere as well.

Feeding Somali children may be saintly; feeding our own children is morally obligatory. Parents may nurture not because it's their duty, they do it because they love their child, but we certainly believe that parents have a duty to help their own children. We have duties of honesty and fidelity in our personal relationships. Our partners are owed this.

The final category of good actions are things we simply ought to do, not because they are heroic or because there is a duty to do them but because it is morally good to do. In this class are some notions of charity—not heroic charity, not giving 50% of your resources—but checking the box on your income tax that will give \$5 to save a tree in upstate New York. These acts constitute being a minimally decent Samaritan, to borrow a phrase from Judy Jarvis Thompson. Most of our lives are filled with acts of beneficence that, though good, are neither owed nor saintly.

Sources of Obligation. There are morally good actions that have to do with other than owings, but we are asked what we owe people with disabilities. One feature of obligations that is of particular importance to today's questions is that there is a finite number of sources of them. If we owe the handicapped anything, those duties must have an origin. What are the sources of obligations? Are any related to the moral claims of the handicapped?

The first source of obligations is our own prior actions. There are three clear and classic examples. If someone makes a promise to do something, the action promised is "owed" the promisee. In the public sphere, Social Security and veterans' educational benefits are examples. In the private, fidelity—keeping one's word—remains a strong duty. Receipt of prior benefits can also give rise to duties, here duties of gratitude. Receipt of social benefits—fire and police protection—is a standard example used by social contractarians in accounting for our obligation to civil society. Duties of gratitude are particularly subtle and interesting in our private lives. To whom do you owe greeting cards or dinner invitations? There is a wonderful sociological literature on reciprocity. The flip side of duties of gratitude are duties of requital, recompense for harm caused. The Veterans Affairs hospital system exists in part to respond to injuries caused to those in military service.

Unfortunately, prior actions cannot account for a general duty toward the handicapped. Some people with disabilities may have been promised assistance (some Medicare recipients). Others may deserve help because we have benefited

from that which disabled them (wounded soldiers). Still others have been disabled by us. Interesting questions arise about duties arising from our responsibility for creating a disabling environment. None of these can account for a debt owed the disabled *simpliciter*.

The second category of sources of obligations is a little abstract, more troublesome, and hence more interesting for philosophers. It has less to do with what we have done than with who we are. Status, not actions, sometimes carries duties. Typically these duties are divided into what are called "natural duties" and "role responsibilities." Natural duties are those incumbent on us simply by virtue of our being a person (nonmaleficence, for example) or because we are in a special kind of relationship. What do family members owe each other? There is often persuasive argument that the notion of duties between family members deems the familial moral relation. The reasons given usually turn on the differences between the marketplace or the outside community and intimate relationships. Discussing this would take us too far afield, though the existence of the debate bespeaks another limitation of norms of debt and owing. The final source of "owings" are those that grow out of relationships we enter or find ourselves in. Here the special duties of citizenship, say, or of being a police officer are found. Again, none of these easily accounts for a debt owed the handicapped in general.

Rights vs Beneficence. Rather than pursue what strikes me as a tenuous case that we owe things to the handicapped, I would prefer to suggest that success in such an enterprise would be pyrrhic. Nonetheless, the desire of advocates for

the handicapped to find a duty-based ethic is understandable. In contemporary culture, claims of beneficence are commonly drowned out by the rhetorical force of rights language. Don't rights trump other moral claims? If so, then rights claimants should be satisfied before we turn to the needs of those with less "forceful" petitions. If we want the handicapped to have a fair chance at social resources, must we not find a right comparable to that of the sick or starving or homeless?

This is a warranted concern, though the claims of the sick, starving, and homeless may be miscast as well. There are genuine, probably insurmountable, difficulties with basing the moral propriety of our responsibility to help the handicapped on what we owe them. Some difficulties are technical. How do we measure the comparative claims of the disabled? How does the source or extent of disability affect the strength of a claim of rights? Do we owe individuals or groups?

These problems are severe but not unique to the claims of the disabled. What is most problematic is that translating the moral propriety of helping the handicapped into claims of right or "owings" lessens the meaning of the assistance for both the Samaritan and the beneficiary. Moreover, it diminishes our moral universe. It translates an act of kindness or decency—helping someone who needs our help—into a matter of desert. Of course we should help people with disabilities, because it is the right thing to do, not because we owe it to them. That this conclusion will strike some as dangerous to the legitimate claims of the disabled shows both the degree to which our moral voices have been narrowed and the degree to which rhetoric has replaced goodness.

Damaged Goods:

Does Disability DisQALYfy People from Just Health Care?

ANITA SILVERS, PH.D.

DISABLED PEOPLE became a barrier to what others regard as a progressive new system for rationing health care with federal approval in 1993 of a waiver of Medicare regulations for the Oregon health plan, proposed in 1992. What gave disabled people standing in this matter is the Americans with Disabilities Act (ADA), which was passed in 1990.

Treating Disabled People Legally

At the federal level, legal assessment of Oregon's 1992 proposal concluded that it violated the civil rights of persons with disabilities, as defined by the ADA. The plan's rationing scheme counted existing or potential disabilities as reasons for disallowing or diminishing medical treatment. The plan thus had the consequence of denying persons with existing or potential disabilities equal health care. In 1993, following a change of administration, the U.S. Department of Health and Human Services approved a waiver for Oregon, but only after central but discriminatory structural features of the plan were removed.

What cannot be ignored about this series of events is that, despite the existence of the ADA, the publicity occasioned by its passage in 1990, and its phased-in implementation beginning in 1991, Oregon's public policymakers did not shrink in 1992 from dictating that having an irreparable disability is sufficient ground for being

denied health care and even life itself. To place the problem in perspective, notice the improbability of these same policymakers permitting themselves to be associated with any proposal incorporating similar exclusions overtly based on race or gender, even though there is ample statistical evidence of the differential effectiveness of some medical procedures by race and gender. This observation is indicative of why persons with disabilities sought and obtained federal legislative safeguards against inequitable exclusionary practices.

The Medically Damaged as Intact Legal Persons. In contrast to the 1973 Federal Rehabilitation Act, with which it shares strikingly similar substantive provisions, the ADA recognizes civil rights rather than bestows rehabilitative assistance. In doing so, the new law incorporates a quietly radical concept: that medically damaged individuals still are intact social or legal persons. Another way of putting this is that, contrary to prevailing assumptions, being disabled does not defeat a person's claims to be benefitted equally. Building this concept into civil rights law deconstructs an institutional framework that has evolved since the thirteenth century to support practices that marginalize the disabled for the profit of other classes of persons. Practices deriving from this framework are especially pervasive in care-giving contexts, so we can expect these practices to be a focus of reform impelled by the provisions of the ADA.

As originally proposed, the Oregon health plan internalized the ancient exclusionary prejudices. It ranked health care as less or more deserved, depending on whether a potential recipient is less or more damaged in any irremediable way. Being impaired in some way that defies medical restoration automatically reduced one's eligibility for all kinds of care, because the sys-

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tem's conceptual framework assumes that to be disabled is without question to live a life of inferior quality.

Celebrating the "Quality of Life": QALY. The original Oregon health plan entrenched this notion by adopting a distributive measure which is supposed to calibrate the quality of lives. Already in use in New Zealand and Australia, this measuring system is called QALY calculation because its unit of assessment is the "quality adjusted life year." The QALY system takes health, defined as the absence of discomfort and disability, to be intrinsically good. Because the goal of health care practice is seen as expunging discomfort and disability, outcomes are judged unsuccessful, and the lives that incorporate them intrinsically not worthwhile, to the extent that they manifest discomfort and disability. QALY calculation constricts our understanding of how life can be valuable in order to weigh it on a scale designed so that the quantity of life can be gauged (1).

On the QALY system, a life expectancy of a year free of discomfort and disability is worth 1 QALY. The more discomfort and disability experienced, the less the year is worth. This system weighs the efficiency of any instance of medical treatment, and sets treatment priorities, by determining its output in QALYs—that is, the probable quantity and quality of the patient's lifespan subsequent to (but not necessarily consequent on) the treatment. A year in the life of a disabled person being worth less than 1 QALY, less benefit is realized from treatment which extends or saves the life of such a person.

QALY calculation thus categorically assigns lower value to persons who happen to be disabled than to able-bodied persons who have identical health complaints (1). The QALY system systematically punishes or deprives those luckless enough to suffer discomfort or endure disability by deprecating their claims for further or better lives only because they previously have been unfortunate. As a social practice, the QALY system further debilitates individuals with disabilities, depriving them of the will to flourish by accentuating the inescapability of the social disadvantage attendant on their physical condition.

Despite these counterintuitive and nonproductive social outcomes, calculating by QALYs is implicit in existing U.S. health care practice. U.S. practice implicitly accepts the original Oregon health plan test for access in all those cases in which a preexisting condition makes a person uninsurable for any health care whatsoever. Additionally, health care providers notoriously make

few accommodations for equal access for persons with disabilities. To illustrate, a much larger percentage of hotel rooms than hospital rooms have wheelchair-accessible bathrooms, although there is no reason to believe that mobility-impaired persons need travel accommodations more than they need health care.

Indeed, devaluing disabled individuals is so pervasive among health care policymakers that discriminatory provisions persisted throughout all revisions proposed by Oregon in its attempts to secure a federal waiver. Ultimately, the federal government was forced to set the condition that certain features of the plan be removed, as a March 20, 1993, N.Y. *Times* story (2) describes:

In setting priorities for healthcare in its *latest* [emphasis added] proposal, Oregon considered whether a particular treatment would remove all symptoms of injury or illness. The Federal Government objected to use of that feature and Oregon agreed to abandon it.

Whether compelled or merely contingently occasioned by the structure of health care practice, assigning lower priority to persons because they are disabled is explicitly outlawed by the ADA. In the ADA, disability is a condition that does not diminish an individual's right to be treated as a fully equal person, a legal assignment of status that runs counter to prevailing prejudice. What the history of the Oregon health plan's formulation illustrates is the entrenched notion that disabling impairments make for generally defective persons, a notion that has been and remains ineradicable. To illustrate, the orthopedist R. C. Elmslie wrote in *The Care of Invalid and Crippled Children in School*, "A failure in the moral training of a cripple means the evolution of an individual detestable in character, a menace and burden to the community" (3). In writing this, Elmslie was supporting a progressive position, for he was in the minority in arguing that crippled children should be permitted to attend school.

The ADA challenges this inveterate attitude by making the right of persons with disabilities to public access identical to the right of other persons. But we should not underestimate how turbulently revolutionary this is, for it reverses practices of segregation and apartheid much more protracted and global than those imposed by race or gender, and it attempts, against the odds, to reform a malignant concept.

According to the ADA, an individual is disabled if unable to perform one or more major life functions due to a physical or mental impairment. That is to say, to be disabled is to be seriously

damaged. But what is the common treatment of damaged goods? Ordinarily, we reject or discard or condemn them.

Thus, even the ADA does not fully avoid the concept that persons so damaged that they cannot perform one or more major life functions should, in the ordinary course of social interaction, expect treatment inferior to or meaner than that afforded others. Nor should the law's framers have ignored this common perspective, for their mission was to devise generic identification of those who, in virtue of being disabled or being perceived as disabled, are further damaged by exclusionary social practices. What the ADA does establish is that systematic inferior treatment of disabled persons is illegal because it deprives them of their civil rights.

Social Costs of Overprivileging Full Restoration. Exclusionary attitudes toward persons with disabilities remain entrenched, as evidenced by the Oregon health plan's persistent devaluing of disabled people's lives and its concomitant overestimation of medical procedures that promise to remove persons from the class of "the disabled." Yet considered against the cost-benefit valuing that governs decisions under the Oregon plan, perpetuating intolerance of disability is singularly costly. Not only does it threaten further harm to already damaged persons, excluding them from social participation and contribution, but it also abets ineffectual rehabilitative procedures. Consider, as a case in point, the Canadian health care system's obsessive drive to camouflage thalidomide children's deficits by fitting them with elaborate but dysfunctional prostheses which were created at great expense to the system, rather than providing a more functional but less cosmetic device. Looking as if they had legs even if they couldn't walk functionally with the mechanical devices was made more important for these children than giving them wheelchair mobility.

This appraisal system was perpetuated in the Oregon health plan. By overprivileging full restoration and disparaging lesser outcomes, the Oregon health plan and other U.S. health care systems tend to inflate expenditures. At the same time, disabled persons' self-esteem is shattered because their requests for equitable, effective health care are met with the prejudice that they are irredeemable medical failures. Moreover, because QALY-type calculation so excessively overrates perfection, it adds to social costs by, for instance, rationing therapy to an able-bodied person to restore the ability to ski instead of to a disabled person to restore the ability to work.

Persistence of Archaic Beliefs. What makes this adverse attitude toward disability so pervasive that legal protection, complete with penalties for violations, is required to initiate equitable treatment for disabled individuals? In antiquity, becoming a slave and becoming disabled through injury or disease were thought of as equally resulting from a person's being offensive to the gods. Thus, archaic beliefs about why individuals become disabled fuel the inclination to avoid them. But whether medical advances in understanding the causes of disabling conditions assist our realistic discernment of persons with disabilities is arguable, for the old attitudes persist in modern health care practice.

Treating Disabled People Ethically

But perhaps this is how we ought to treat people with disabilities. Despite being reminded of the protective provisions of the ADA, the Oregon policymakers who persisted in incorporating discriminatory structural features into their health care plan appeared to be unshakable in this view, for it took direct intervention from Washington to prohibit them from using disability as a justification for deprivation of care. It can be and often is argued that, despite the ADA, the well-recognized archetypes of moral and social obligation do not apply to the disabled. Both moral judgment and social policy typically are formulated against a standard of normalcy. Yet our unrelenting conception of those who are disabled is that they are abnormal. A popular view is that disability alters people to such a degree that their singularity defeats moral or social protection.

To see why, consider extending impartial treatment, usually assumed to be a cornerstone of ethical behavior and social justice, to persons with disabilities. To act impartially is not to privilege anyone's special point of view. So to act impartially to me, you must balance your standpoint, with its special interests and needs, by giving equal weight to what I want you to do, from the viewpoint of my special interests and needs.

This is rational, for how can you justify any conduct toward me which you would object to were you in my place? Of course, you can't really know what it is like to be me, so the mental exercise here is to abstract by considering what persons' ambitions normally would be were they in my place. Thus, the normalizing imagination operationalizes impartial judgment.

This means that, to reason morally, you must

imagine what it is normal to do in my place. But you cannot, for being disabled is inherently unthinkable for those who are not so. You can imagine many states of being which you have not suffered or enjoyed, but experience gives no basis for accurately imagining being unable to perform a major life function. Performing major life functions is so intimate an element of the fabric of our experience that one simply cannot accurately conceive of how to live without them.

Treating Disabled People Caringly

So, it is argued, being disabled so severely reduces what one has in common with normal people as to render ethical systems based on reasoning of the Golden Rule type ineffective. An often-cited condition in rational moral systems is that reasons for action must not be opaque to normal adults. For a moral reason to have motivating power, moral agents must understand it, grasp it, or get it. If a "normal" individual cannot grasp realistically what it is like to be in a "damaged" individual's place, then truths about how one would want to be treated if one were disabled are opaque to normal individuals and cannot motivate them morally. What obstructs ethical thinking here is that reasoning responds to the common, not the deviant, case.

Moral Deficiency and Empathy. But if reasoning fails, perhaps feeling, particularly caring feelings, will prevail. In an influential essay in which he attempts to reflect common points of view, the philosopher Lawrence Blum argues along this line (4), maintaining that we are morally deficient unless we respond empathetically to the situations of persons with disabilities. Patterning his account on an actual case, Blum describes a supervisor, Theresa, who accepts her company's legal obligation to accommodate to the disability of an employee, Julio, but who

offers Julio less than he needs and is entitled to. . . . It is not that Theresa fails entirely to see Julio as "disabled" and as "in pain," but she does fail fully to grasp what this means for him and fails fully to take in or acknowledge that pain. . . . Theresa is failing to perceive or acknowledge something morally significant—namely, Julio's physical pain and his distress at the impact of his condition on his work situation (ref. 4, pp. 704–705).

Blum's verdict grows from his conviction that logic-driven judgment stumbles where agents must be just or otherwise ethical to persons less advantaged than themselves. Rather than trying to judge impartially or categorically, Blum in-

sists, advantaged agents should be so sensitive that their perception of the particularities of any situation matches that of whoever may be victimized by it.

Blum attributes impaired moral vision to emotional blockage against certain threatening aspects of moral reality. Advantaged persons dread beholding damaged persons out of fear that in future they might themselves become impaired. But "blocked" moral agents are not incurable. Blum comments, "Theresa may need to work through—perhaps in some form of therapy—her deep and partly unconscious association of physical pain with weakness" (ref. 4, p. 718).

Why is Theresa so morally miserable as to require therapeutic intervention? At various points, Blum levels different charges. First, we learn that she offers Julio less than he needs and is entitled to. But Theresa surely cannot owe Julio everything he needs. Legally, she need offer only what is required for him to do his job, as long as the cost of accommodation is not unreasonable when compared to the employer's entire budget. Moreover, even on the most indulgent needs-based model of moral and social justice, it is irrational to demand for everyone everything they need, since satisfying some needs may prevent satisfying others.

And if Julio is being denied what he is entitled to, his remedy lies in legal enforcement, not in Theresa's moral renewal. No one would seriously propose that moral rehabilitation of armed robbers should substitute for their arrest. Nor should persons with disabilities tolerate less than the legal protection of their legal rights. Theresa ought to comply with both the letter and the spirit of the law, but she owes this conduct to her employers as much as to Julio, and her obligation is directly in virtue of Julio's specific legal rights, and only proximately in virtue of his being disabled.

Next, Blum accuses Theresa of failing to acknowledge the impact of Julio's pain and despair on his work. But this begs the question, for Theresa finds these thoughts out of place in her professional interactions with Julio, except to the extent that there are reasonable accommodations she can make which will permit Julio to do his job despite his pain. Blum's issue is not whether Julio actually is in pain but instead whether Theresa has an obligation to require less of Julio than of his co-workers in recognition of the debilitating psychological impact of his physical state. Blum thinks she owes this forbearance to Julio.

"Owing" Indulgence and Sympathy. But no law requires Theresa to accept work from or apply

lesser standards to Julio because he is disabled (although she does have the burden of proof that her standards are entailed by the essential functions of the job). So if Theresa owes Julio any indulgence, the obligation must be ethical in nature, not legal, and it must derive, according to Blum, from her genuinely regarding Julio's disability.

It is commonly supposed, and just as frequently resented, that persons with disabilities must be indulged. Blum's thinking here is illustrative. He assumes, but does not demonstrate, that to acknowledge another's pain is also to accept the pained person's estimation of the incapacitating impact of the pain. If Blum is right, to block regard of another's pain is inescapably morally perverse because only if natural sympathy is pathologically blocked could one be intolerant of a person in pain.

In Blum's view, it is natural to recognize the reality of others' pains, even if one cannot imagine feeling them. Other people's pain is invisible only to the morally blinded. Because Julio's debilitating despair is real, Blum addends, Theresa should credit it. In other words, it is only Theresa's impaired perception which blocks her from assenting to Julio's assessment of himself. But is this so?

I do not think it can be so, for to condemn Theresa's moral proficiency in this way has a bizarre implication. A common experience in learning how to be disabled is to regret, when looking backward, one's initial debilitating panic and abdication. This process is recounted again and again in anecdotal and autobiographical material written by persons with disabilities. On Blum's account, which for this reason cannot be right, persons reconciled to their disabilities must be guilty of moral insensitivity to themselves.

But it is absurd to think that disabled persons' earlier despairing states always are opaque to their later, more hopeful selves. Nor do disabled persons owe it to their earlier selves to regard self-pity as credible. Analogously, Theresa owes Julio no validation of his suffering.

But does Theresa owe it to Julio to be sympathetic? Blum seems to think she does, and that Theresa is obligated to seek therapeutic intervention so as to be able to feel for Julio. To put it mildly, this is a curious claim. Blum does not recommend therapy in any of the other cases of failure of moral perception he examines. Why should those unsympathetic to victims of racism be ostracized, but those unsympathetic to disabled persons be psychoanalyzed? Moreover, why does Theresa owe it to Julio to cure herself of her cold-

ness, for their relationship goes no further than the workplace?

As we have seen, Julio's pain is separable from its debilitating impact. The latter is the outcome of Julio's cumulated history, his expectations, his models of behavior. A later Julio, with changed experiences and values, may well react differently to Julio's pain, suffering being an inoculant against itself.

There is a logical flaw in thinking that Theresa owes either the despairing or the sanguine Julio acceptance of his own assessment of the quality of his life. No more does Julio owe Theresa or any other nondisabled person acceptance of their assessments of the quality of his life. But if the particularities of a real disabled person's happiness or suffering are elusive in fact, they are fictionally well-known. Both Theresa and Blum, and the QALY measuring system as well, accede to entrenched illusions about who disabled people are or ought to be.

A review of the social history of disability explains why there is social pressure to be especially caring to the disabled; a historical process makes the disabled both a protected and a disposable class. In condemning Theresa for omitting what she has no duty to do, Blum demands from her dispositions summoned by the professionalization of caring.

Institutionalizing Caring

Persons with disabilities are the subject of many dangerously deceptive mythologies. To accede to these is to place disabled and able-bodied persons equally at risk. One of these inventions, accepted by Blum in condemning Theresa, is the notion that persons are owed exceptional treatment in virtue of being disabled.

This curious and potentially expensive thought arises from our conflicted perspectives on disability. It ushers in what philosophers call a straw man, a position so soft it is easy to blow away. This maneuver is typical of discourse about disabled people, where proponents and opponents both habitually substitute the extreme case for the central one. In what follows, I try to untangle some of the strands of our conflicted thinking about being disabled by examining some hard historical facts.

Seeing the Disabled Clearly vs. Looking Away. But, as with much else about disabled people, a natural reaction to seeing them clearly is to want to look away.

This response is inveterate. Events at the conference entitled "What Do We Owe People

with Disabilities?" at which my original presentation of this paper was made illustrated the tendency. A professor of pediatrics perceptively described certain ethical dimensions of the behavior of staff in the case of a child born with a life-threatening respiratory condition. Staff was insistent on securing reparative surgery for the child, despite the very high mortality rate and high cost of the procedure. The surgery was not performed but the child survived. At three months, it became clear that the child had other physical problems which made him paraplegic (but did not affect him cognitively). Two years later, the same staff who had urged a dangerous, expensive procedure in the belief that the child could be fully restored objected to much simpler, less costly procedures for a child they now viewed as being irreparably impaired. A discussion about whether a paraplegic two-year-old's life and future were valuable enough to deserve health care ensued.

No one seemed to be concerned about the presence in the audience of an individual with a condition very similar to the child's. It is inconceivable that the discussants would question whether persons of a certain race should receive life-saving or other medical care when persons of that race were present. Yet some in the audience insisted that individuals with a certain disability should be denied life-saving care in the face of someone with that disability. That is, they did not hesitate to express the view that a member of the audience was not worthy of life in virtue of being disabled.

An earlier example: in 1797 the philosopher Jeremy Bentham devised a plan for segregating residences so that lunatics would live only with the deaf, who would not be disturbed by the madmen's howls, and the lame would live with the blind, who would not recoil from their deformities.

In fact, only recently has the legal climate contravened rather than authorized such reactions. The often-cited City of Chicago ordinance barring maimed, mutilated, or otherwise deformed individuals from public ways or other public places is not unusual. And although such laws have ceased to be enforced, the impression remains popular that only on sufferance may persons with disabilities occupy public space.

Physical Functioning and Social Functioning. But although the inescapable fact that disabled persons are damaged prompts malign treatment, just as bleeding chickens are pecked at by their flock, this is not the only natural reaction to them. In certain close-knit traditional groups, the

reverse is the case; a community member's disability may go unremarked. Commenting on the tendency in tradition-governed groups to perceive individuals in terms of their roles rather than their personal traits, the philosopher Alisdair MacIntyre tells about the schoolmistress in his father's village who wrote on the blackboard with her foot because she had been born with no arms. Since there was no other teacher, the schoolchildren believed that while pupils labored to write with their hands, teachers were so skilled they could write with their feet. (MacIntyre made this point at a session organized by the A.P.A. Committee on Blacks at the 1990 American Philosophical Association Eastern Division Meeting.)

Note that the children perceived the teacher not as a material but rather as a social entity. Nor should it surprise us that someone defective physically may yet be effective socially, for we have a much greater repertoire of social functions than of physical ones, and more flexibility in performing the former than the latter. (Parenthetically, one way to conceive of A.D.A. is as bestowing the right to choose which physical functions to use to execute a social function. We shall return to this point in the last section of this essay, where I introduce the "principle of functional equity.")

Ethics of Caring vs. Ethics of Owning. Proponents of the ethics of caring, which is contrasted to the ethics of owing, argue that social intimacy or closeness between persons, originating from the natural affection felt by parents for their helpless young, is the foundation of morality. As the young mature, their natural feelings of gratitude to their parents make the relationship reciprocal. Eventually, practice and perception extend caring along a network of nonfamilial affiliations until a moral system evolves. Thus, it is argued, ethics is the extension, through social artifice, of those feelings which bond individuals into a functionally protective group. The 18th-century philosopher David Hume depicts these extended trusting relationships as an "artificial contrivance for the convenience and advantage of society" and as requiring constant education and effort to maintain (5).

On this account, the foundational moral attitude is trust, which is the feeling inspired by principals of families in their dependents. It is the mechanism for cooperative family efforts, and, having been learned at our mothers' knees, as it were, it can be made to operate among the members of society to secure for all citizens the protective, nurturing climate achieved by the functional family. On this analysis of moral and social mechanisms, basic moral and social relationships

are not between equally secure, autonomous individuals but between dependents and those on whom they must rely.

Within a family, one progresses ideally from cared-for childhood through caring adulthood to cared-for old age. Within a functional family, defects in persons cause them to be cared-for rather than condemned. Indeed, a main objective of family structure is precisely to render this kind of care. So if we understand moral or social bonding to be an expansion of the attitudes which suit us to function within the family, we should expect to have prohibitions against, or at the very least reservations about, behavior which threatens those who are dependent. This would explain why Blum is so disquieted by how coldly Theresa is disposed toward Julio.

If moral and social operations are expansions of basic caring, it should be no surprise that whether someone treats the disabled caringly becomes a test of that person's trustworthiness. For whoever treats the disabled badly is easily seen as deficient in those dispositions that all of us in a generalized way rely on in others whenever we are vulnerable to them. So we can see why adverse treatment of disabled persons, though a natural material reaction, is deprecated in accounts like Blum's that take another natural response, caring, as the foundation of moral and social value. It is not that the object of the treatment is owed better, but that agents who treat dependents uncaringly appear for that reason disposed against treating anyone well. Utility here makes protection of the vulnerable not an obligation, but instead a socially salutary disposition, as the social history of disability illustrates.

The Social History of Caring

Beginning in antiquity, persons with disabilities were portrayed as unique and solitary. Not until the 13th and 14th centuries do they begin to be systematically referred to as a social group. The context in which this change occurs is illuminating.

With the breakdown of the feudal system, laboring people gained geographic mobility, yet the need for place-bound laborers remained pressing. Consequently, laws were enacted which forbade able-bodied lower-class persons from traveling from town to town without special authorizing documents. But disabled individuals, the exception, were encouraged to travel from town to town to afford relief from their protracted presence. From the point of view of the able-bodied, this provision could be viewed as a dispensation to a

privileged class, while the same differential treatment appeared to the disabled to be a mechanism for expelling them from the ranks of workers.

Modernizing laws reconceived persons with quite different disabilities by grouping them into a single inferior class, one which the dominant class, for its own advantage, treated exceptionally—consequently exciting the envy of other subordinated groups. From this institutionalizing process emerged the concept of "the disabled." Simultaneously, groups like the guilds of the blind, who joined together to hire guides, work at certain crafts, and visit the sick—a 14th-century precursor of the Independent Living concept—disappeared (6).

The Deserving Poor, Professional Care, and Dependence. By the 17th century, the virtue of according charitable benevolence to those in need clashed outright with the fear of creating a class of drones. Consequently, there emerged the concept of the "deserving" poor, those who would have worked but for their unfortunate impairments. To be a member of this class was to be distinguished from the undeserving, willfully malfunctioning poor, although, as we have seen, careful attention to character was mandated to keep a disabled person from slipping over the line.

By definition, then, the deserving poor were incompetent. Their treatment, although technically benevolent, was designed to make their condition seem unattractive to those capable of work. In view of their definitively deficient state, the deserving poor could not be conceived of as themselves capable of the responsible use of whatever means charity bestowed on them. Consequently, there emerged another social group, care-givers, persons whose profession it became to channel charity by administering it properly to damaged individuals. Thus, as a social class, the disabled became required by definition to be nonproductive. They also became the means of production for members of another group, professional care-takers.

These conceptions, and the institutions they informed, forged conflicting imperatives. To demonstrate their commitment to contain the costs of benevolent practices, to discourage deceptive drones, and to prove their competent professionalism, care-takers needed to alter some of their charges to the extent that those charges no longer required charity. But to mitigate the risk of rehabilitation depleting the supply of those who need caring for, care-takers kept finding that some types of persons had been mistakenly assigned to the class of undeserving poor because

they were in fact involuntarily rather than willfully defective.

To shift subjects from being viewed as responsible for their defects, and therefore underserving, the medical model is typically invoked. So, for instance, alcoholism is said to be a disease instead of a choice. When caring-for is no longer an expression of personal attachment but has become a livelihood, the prospective liberation of disabled persons from their submissive state of compliantly being cared for cannot help but occasion defensiveness in their care-givers.

Just as those who believe in devils pressure wrongdoers to act possessed, the social identity of care-givers forces care-users to acquiesce to dependence. Robert Scott's study of the blind shows how agency-dependent blind persons are conditioned to be docile, acquiescent, even ascetic and melancholy, by social acquaintances as well as agency personnel, regardless of whether these traits are advantageous for survival outside the agency setting (7). But that our institutions impel us to expect disabled people to be dependent does not preclude its being wrong to do so.

The Ethics of Caring

Contemporary critiques of modern moral thought, particularly those which claim to substitute a feminist for a patriarchal point of view, often cast moral motivation on the model of personalized family feeling and reject the depersonalizing process of impartial judgment. Notice, however, that tender feelings for familial dependents are not infinitely extendable to total strangers. Animals typically nurse only their own young, shunning even these when the young acquire an alien scent. Parents notoriously are blind to the failings of their own children while reviling the self-same behavior in other people's children.

Consequently, it is incumbent on those relying on nonfamilial protection to conduct themselves in general so as to stimulate protective behavior in others. Nevertheless, a dependent stance is advantageous only if genuine—that is, if the putative dependent is truly incompetent. But in a social system in which caring-for is the primary way the able-bodied relate to the disabled, it is socially incumbent on the disabled to profess incompetence even where they are more competent than the able-bodied. Not so very long ago, women were expected to dissemble this way to men.

This kind of system readily lends itself to harming the putatively dependent by requiring

them to accept care of lesser quality than what they could administer to themselves. This dilemma is captured with exquisite painfulness in the silent comedy scene in which the bumbling comic drags a blind man away from his bus stop and across the street, repeating this action with self-congratulatory zeal each time the recipient of his care makes the hazardous journey back across the street. The joke lies in how the comic's self-importance undercuts his every effort to be virtuous. The tragedy lies in how the scene belittles the comic character's craving for admiration, but is unconcerned about his placing a disabled person in jeopardy. The characters who tie Pauline to the railroad track are seen, in virtue of that act, as villains, but the character who places a blind man in equivalent peril is not seen as villainous, because caring is regarded as self-justifying, however endangering it may also prove.

Surely, some of us are not obligated to let ourselves be harmed simply to afford others opportunities to be virtuous. Is it reasonable to insist that some citizens must voluntarily be poor only because the rich need the opportunity to act charitably, or that some persons are obligated to expose themselves to criminals to give the police somebody to rescue? Yet modeling morality on being cared-for and being caring appears to make such self-sacrificially compliant behavior obligatory for persons with disabilities.

Fairness Reconsidered: The Functional Equity Principle

This line of thought reveals that when caring is institutionalized, whether socially or ethically, persons with disabilities are deleteriously designated as dependent. Capitulating to this role even when doing so is injurious becomes a prerequisite for being treated ethically. But this seems to be an oxymoron, for the price exacted for better treatment cannot be that one is treated worse.

Notice that to understand this last argument, we do not need to entertain the impossible thought of imagining one's self to be in an unimaginably bad circumstance. For it is not so difficult to ascertain what we ourselves do want in respect to being harmed by others' incompetence, however well-meaning. Nor is it so difficult to apply this kind of knowledge predictively. Let us explore this methodology, which applies what I call the principle of functional equity. This principle is formulated to reflect a legal right established by the ADA: the right of individuals, if barred by physical or mental impairment from performing social functions in the ordinary way,

to exceptional but equivalently efficacious modes of performing these functions.

Functional Access. What is it you want to have functional access to? What if all those competing with you for employment had access to telephone equipment but you, totally arbitrarily, did not because the telephone company did not consider you part of the public whom it is obligated to serve? What if you, alone, were denied access to all broadcast information? What if you alone were forbidden the pavement and forced to trek in the midst of the vehicle traffic, while everyone else walked in safety?

That we have public utilities commissions to maintain people's access to phones, a Federal Communications Commission to maintain access to broadcast information, and street building programs to provide safe walkways demonstrates your wants, as well as other people's, in regard to the desirability of these public benefits. Consequently, if some among us are to be denied such access, the burden of proof lies not in imagining how it would be to be disabled, but in imagining why being disabled would eliminate normal wants—to communicate, to be informed, to move safely about a city, or to receive health care or maintain life itself.

This test immediately disqualifies the QALY measurement system. For the scale on which a disabled life is devalued was devised by asking able-bodied people to hypothesize whether they would rather live with a disability or die. That their testimony expresses the myths about disability rather than empirically confirmable wants is evidenced by the lack of power of the QALY system to predict the actual behavior of persons with disabilities. The suicide rate among persons with disabilities would be much greater than it is if the QALY system reported actual preferences instead of fearful fantasies.

Normalizing on Deficit. If impartial judgment abstracts toward standardized ability, as is inherent in the hypothesizing process used to calibrate the QALY scale, it can neither establish nor excuse obligations to persons with disabilities. But what if it abstracted instead toward deficit? This would mean setting as a standard not what is preferred by those who are perfect or normal, but rather what would remain desirable were one to be impaired.

We are so institutionally focussed on the disconformities of persons with disabilities that we do not consider to what extent it is rather the environment which disconforms. But if we are not normalizing toward perfection but toward deficit instead, the question of past repressive actions

which shaped a defective social environment for persons with disabilities is inescapable. The ease with which accessible designs are instituted if required, and the absence of good reason for past failure to do so, shows what could so easily have been done were being blind, or hearing impaired, or unable to walk the central rather than the excluded case. But there are powerful interests with more to gain from suppressing disabled people than from liberating them.

Evidence of these comes easily by examining institutional conduct subsequent to the Federal Rehabilitation Act of 1973. For example, for at least a decade after its passage, and even today, institutions receiving federal funds, and thus constrained to do otherwise by the law, proceeded with construction in violation of it, and then retrofitted, the advantage being that segregating rather than integrating design and building preserved the economic advantages of treating disabled persons exceptionally. In public building it became standard practice to erect an entrance with steps and then to add a ramp at extra cost from special funds, instead of specifying the inclusion of ramps to be built at no extra cost from the initial design. A recent example is the architecturally acclaimed Pittsburgh airport, opened in 1993, which at this writing requires persons in wheelchairs to use toilets in full public view because the bathroom design precludes installing doors on the wheelchair-accessible stalls. The taxpayers' cost to remedy these unlawful facilities may be considerable.

The irrationality of such social patterns, absent hidden forces, suggests that segregating disabled persons is engineered, not accidental. The case for affirmative social action to redeem past repressive acts is thus at least as strong for persons with disabilities as for members of other protected classes.

We cannot predict who will be deficient and in what respects. We surely cannot predict whether we ourselves will in future become defective, either traumatically or in the natural course. "The disabled" is a fluid group, its ranks continuously replenished by those who previously shunned its members. Nor can anyone be sure he or she will not join those ranks.

With this in mind, we can see that prudence, itself a virtue, advises rules of conduct that normalize toward deficits, for these are in the best case neutral and in the worst beneficial, whereas normalizing toward perfection is in the best case neutral but in the worst destructive. Thus, a lucid recasting of the question "What do we owe persons with disabilities?" might be "What do we

owe our possibly future selves?" Each affirmative action to increase accessibility not only remedies the past exclusion of some people, but guarantees all people an increased prospect of maintaining their social function should they suffer physical or mental damage.

Accessibility of Health Care and Functional Equity. From this new perspective, let us consider whether health care must be made accessible. Normalizing to deficit rather than to perfection discloses why QALY measurement fails morally as well as legally. The functional equity principle requires practices to be responsive to the standard of actually exhibited rather than suppositional wants. Thus, in general, if nondisabled persons want effective and cost-effective personalized health care, and this functional desire is satisfied for them, the burden of proof for denying equal treatment to persons with disabilities lies in showing why having a disability eradicates this want.

Because the functional equity principle relies on actual rather than hypothetical wants, it rejects the familiar argument that the QALY system is fair to persons with disabilities in that, although they do worse on it if their lives are at stake, they do better just in case they can be cured. What is crucial to the functional equity principle is that it shifts the burden from proving that, despite a disability, a person should be treated equally—a burden borne by the disabled person—to proving that, because of a disability, a person should be treated differently—a burden borne by whoever tries to exclude the disabled person. Thus, this approach begins by adopting the ADA's revolutionary assumption that, despite being medically damaged, disabled individuals are intact social and legal persons who do not need to prove their claims to benefits others collect without special justification.

Such a policy protects nondisabled people by extending their access to health care should a disabling condition commence. It thus offers equity in, as well as from, institutionalized health care. At the same time, costs are contained because the functional equity principle focuses institutions on what is practical rather than hypothetical.

The functional equity principle prohibits using as a standard what nondisabled persons fantasize

they would want were they to become irreparably damaged. Moreover, under it, treatment of disabled persons operates as a benchmark against which to test the efficacy of healthcare practices, for a system which serves equitably those who stand witness to the system's limits is a robust system. In view of the administration's conditions for granting a waiver to the revised Oregon health plan, such considerations promise to constitute a prominent legal test of the legitimacy of implementation provisions under the plan.

A final admonishment: there are some kinds of cases the functional equity principle cannot decide. It cannot be applied wherever nondisabled persons' wants are so diverse as to defy empirical normalization. So, for instance, it cannot solve the problem of whether disabled persons should be assisted to die, since we cannot normalize able-bodied people's wants about this. Nor can it illuminate what to do about vegetative individuals, ones who truly have no wants at all. These individuals are nonstarters for this account because they are not persons with disabilities, because they do not seem to be social persons at all. Extreme or borderline cases are just that, and we must be on guard against putting them in the foreground in these discussions, for to do so is often just another manipulative device for prolonging the invisibility of people with disabilities.

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Cases and Doubts

IAN R. HOLZMAN, M.D., AND JOSEPH V. STILLO, M.D., PH.D.

A Case in Neonatal Ethics Ian R. Holzman, M.D.

A 2900-gram, full-term infant was born at a large city hospital. His family were recent immigrants from Chile and were unemployed. They were religious and very committed to each other and their child. The prenatal history, labor, and delivery were all unremarkable. Although the Apgar scores were 7 at one minute and 8 at five minutes, he was noted to have marked chest retraction and inspiratory stridor after birth. His nasal passages and oropharynx were fine, but attempts at intubation revealed an obstruction below the vocal cord. A chest radiograph suggested a narrow trachea to the level of the carina. He was transferred to a tertiary care center, where a computerized axial tomograph showed diffuse tracheal stenosis for the entire length of the airway. With the application of nasal continuous airway pressure and 30% oxygen he was able to maintain adequate ventilation and oxygenation.

After thorough examination, consultation, and a literature review, the parents were presented with the following situation:

- This condition is usually fatal during the first year of life but is uncommon enough to make hard and fast predictions difficult
- A procedure performed in a few cases has been described for attempted amelioration involving

surgery under deep hypothermia. The entire trachea is exposed and the cartilages are cut posteriorly. The success rate is unclear, and prolonged hospitalization, reoperations, infections, and other effects are likely.

- To do this procedure, the infant would have to go to a city 700 miles away and remain there for a prolonged period.
- The alternative is to keep the child on airway support and to observe the natural course, leaving open the option for surgery in the future.

The family chose the last option, and the child remained in the neonatal intensive care unit with nasal continuous airway pressure support for many months. The parents did agree to a "do not resuscitate" order, which was never actually an issue. There were periods in which the infant's respiratory distress became fairly severe, but he was manageable medically. It was possible to nourish this infant, and he did begin to grow. At between 3 and 4 months of age, he was seen to have short proximal arms and legs, and the diagnosis of a particular dwarfing syndrome that includes abnormalities of the trachea as well as other cartilaginous tissue was made.

Throughout this period no attempt was made to insert an endotracheal tube or to perform a tracheostomy, since the tracheal condition was diffuse, but when the infant was 5 months old, during a period of distress, an endotracheal tube was inserted, bringing marked relief of the distress. A tracheostomy was then done and arrangements were made for home care. The father found employment with one of the other families in the intensive care unit and the mother spent many hours learning to care for the infant, who continued to have respiratory exacerbations.

At 18 months of age this child had evidence of some developmental delay but was exceedingly pleasant and responsive. Although he could not

Adapted from presentations at the medical ethics conference "What Do We Owe People with Disabilities?" March 5, 1993, Mount Sinai Medical Center. From the Department of Pediatrics (IRH) and the Department of Rehabilitation Medicine (JVS), Mount Sinai Medical Center, New York City. Address reprint requests to Ian R. Holzman, M.D., Professor of Pediatrics, Box 1513, Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY, 10029; and to Joseph Stillo, M.D., Ph.D., Medical Director, Bacharach Rehabilitation Hospital, 61 W. Jimmie Leeds Road, P.O. Box 723, Pomona, NJ 08240.

walk, his upper body skills were developing quite nicely, including throwing a baseball with great accuracy. The family were not unhappy with the outcome, although it had altered their lives. They felt they had made the correct decision.

A Case in Rehabilitation Ethics

Joseph V. Stillo, M.D., Ph.D.

This case report from the Department of Rehabilitation Medicine at Mount Sinai Medical Center was derived from a review of the medical records, as well as interviews with most of the treatment team members, including home care staff and family.

A 22-year-old man was brought to an emergency room in Yonkers, NY, in November 1991, comatose after being assaulted with a baseball bat while he slept in his girlfriend's apartment. In the emergency room, he was intubated and placed on mechanical ventilation. A CT scan of the head revealed right frontal lobe hemorrhage and bilateral subdural hematomas. He was treated nonoperatively with steroids and Mannitol for cerebral edema, as well as later for pneumonia and urinary tract infection. He awoke after a few days, although sedated, and was weaned from the mechanical ventilator after 10 days. He was maintained on phenobarbital and dilantin for seizure prophylaxis. His generalized response to stimuli gradually increased, and after 6 weeks he was referred to the Inpatient Rehabilitation Unit at Mount Sinai for rehabilitation. At the time of referral, information from the medical record, as well as directly from the referring neurosurgeon, indicated that the patient was blind, had right hemiplegia, and was confused and agitated, but able to give an agitated response. He required condom drainage for urinary incontinence and maximal assistance for his activities of daily living.

A series of meetings and telephone conversations with his mother showed her to be someone who seemed committed to her son's best interests; she was a strong advocate for his admission for rehabilitation. She offered the following social information about the patient:

- He was unmarried, the father of three children, ranging in age from 4 to 7. He had no contact with the children or their mother.
- He was a high school dropout.
- He had a long history of drug (mostly cocaine) abuse.
- His mother had three other children at home, aged 20, 15, and 2.

His mother attested repeatedly to her desire to take him home after his rehabilitation. He was admitted to the Inpatient Rehabilitation Unit at Mount Sinai on January 30, 1992.

On admission, he was thin, with extremely low vision, able to localize sound but only able to see shadows; his sense of smell was decreased. Motor deficits included a very weak right leg with increased tone and a plantarflexion contracture. Upper body strength and range of motion were within normal limits.

A mental status examination revealed that he was not oriented to place or time and only intermittently oriented to self. He followed simple commands and was able to point to body parts with 50% accuracy. Speech was fluent, but he displayed severe word retrieval difficulty and paraphasic errors. His verbalizations were frequently inappropriate and perseverative. He was intermittently agitated, especially when confronted with complex commands or environmental stimuli. Cognitive dysfunction spanned all domains tested, including sustained attention and concentration, span of immediate and delayed recall, and simple problem solving. He required constant redirection to attend to a task and continuous verbal cues to sequence.

Functionally, he had difficulty orienting his body in space; he required moderate assistance to stand, including feet positioning. On standing, he displayed bilateral clonus with flexor withdrawal on the right. He required moderate assistance for balance and tended to retropulse. EEG showed diffuse low voltage, and visual evoked potentials were absent on the right and extremely attenuated on the left.

His admitting diagnosis and disability was traumatic brain injury, categorizable as level IV in the Rancho Los Amigos Cognitive Scale (confused and agitated, with short attention span and decreased ability to process information; confusion may lead to behavior requiring specialized management). In addition, he had right lower extremity spastic plegia.

He was placed on an intensive multidisciplinary rehabilitation program of individual and group behavioral and cognitive remediation. The goals were to increase his orientation and cognition, independence in activities of daily living and self care, independence in ambulation with a cane and a short leg brace, discharge to the community, exploration of vocational or prevocational options, addressing his drug abuse issues, and assisting the family and the patient to develop realistic goals on discharge. Rehabilitation physicians and nurses, psychologists, physical and

occupational therapists, a speech-language pathologist, vocational rehabilitation counselors, therapeutic recreation therapists, and social workers were all involved. Consultations were obtained from neurology, psychiatric clinical-liaison, and ophthalmology. Pharmacologic adjuncts to control behavior included Nadolol and Haldol, and anticonvulsant therapy was changed to Tegretol.

The ophthalmologic evaluation revealed bilateral vitreous hemorrhages. Because of little spontaneous clearing, he underwent vitrectomy on the left eye, with significant return of vision in that eye.

Vocational rehabilitation intervention revealed that he had dropped out of school at either the 8th or 9th grade level after his girlfriend's first pregnancy. He did not find employment until two years later. Further history obtained from his mother revealed that his behavior in class was characterized by his teachers as "volatile." He held positions as a stock clerk and shipping and receiving clerk, but the duration of each of these period of employment was short lived because of drug abuse and absenteeism. He had applied to the U.S. Army, but was refused because of a seven-year history of cocaine/crack abuse and lack of a GED.

Generally, he showed considerable improvement across all domains of his function, including mobility and cognition, and he was discharged on May 7, 1992, approximately three months after he was admitted to the rehabilitation unit, and less than six months after his injury.

His status on discharge was as follows: his cognitive status can be described as a combination of level VI and VII of the Rancho Los Amigos Cognitive Scale. He was cooperative, motivated, and goal oriented, with fair insight into his cognitive deficits; he had significant resolution of his disorientation and confusion; he displayed increased attention and immediate and delayed recall, and decreased distractibility. He exhibited temporal and spatial orientation with good consistency. He was generally oriented to place and people, but needed frequent orientation to day and date; he was able to recall events of the previous day with minimal verbal cueing; he was still easily distracted in social settings, but did better in secluded environments, able to focus on tasks for 20-30 minutes; his problem solving ability was fair, and his judgments and safety awareness were good.

He was independent in self-care activities, including showering and shaving; he was able to do simple arithmetic and make small purchases

and to use a magnifying glass, which assisted him in using a telephone with supervision. He had good standing and sitting balance and was independent in walking with a cane and a solid ankle orthosis for a distance equivalent to 5 blocks in familiar environments on level surfaces, but he required supervision because of his visual and spatial disorientation. The only durable medical equipment he required was a tub-shower bench and a cane.

He was discharged to his mother's home with a home health attendant for 8 hours a day, 7 days a week. One week later he began participating in a multidisciplinary outpatient program at Mount Sinai, and he was given follow-up appointments in the rehabilitation and ophthalmology clinics. Medically, he displayed continued resolution of his vitreal hemorrhage, and the last examination showed that he had 20/50 vision in his better eye. He required close supervision to assure that he took his anticonvulsant medication, and he frequently ran out of his medication.

His outpatient program consisted of occupational, physical, and speech therapy, neuropsychology, a leisure planning group, "group think" sessions, vocational counseling, and social services. Transportation to and from Mount Sinai was via ambulette. His attendance at these programs was fair but occasionally inconsistent as a result of ambulette difficulties. After three weeks, he was independent in walking without the cane, but still required the short leg brace and supervision in unfamiliar environments. He was cooperative and nonagitated, and for the next four months showed improvements in problem-solving skills, although his approach was very concrete. He was frequently tearful and reported feelings of anger and remorse bordering on self-abuse for the occurrences that led to his traumatic brain injury. His daily program was aimed at increasing his organizational skills and adjusting to lifestyle changes brought about by his brain injury and its impact on work and school reentry. He demonstrated improvements in arriving at group classes on time and preparedness in using his daily planner as a compensatory strategy; social skills were good; he required moderate assistance for identification of his leisure interests. There was a strong suspicion that he had resumed using drugs and drinking.

On October 5, 1992, five months after his discharge from the Inpatient Rehabilitation Unit, he and his attendant arrived to see his rehabilitation psychologists with his belongings. He said that his mother had locked him out of the apartment and left for California. Numerous attempts were

made both by the rehabilitation and the home care staff to secure lodging for him. His father and grandmother refused to provide lodging, and he left with his attendant without a clear resolution of the problem. He was referred to the Protective Services Administration, but was rejected because "patient has a mind of his own, and he can do what he wants." The home care social worker filed a formal complaint. Four days later, the rehabilitation social worker located a friend who provided him with lodging. The home care unit was unable to provide further service because he lacked a permanent address. His Medic-

aid benefits expired that month, and he has been lost to follow-up.

In March 1993 his mother informed me that he had been driving her crazy before she locked him out. She had gone to California for two weeks and on her return, he had moved back in with her. In January she requested long-term placement for him, and an application is currently in progress for long-term placement in the Commonwealth of Massachusetts. He has been living with his father for the past two weeks. He is scheduled for follow-up in the rehabilitation clinic in two weeks.

What Do We Owe People With Disabilities?

Moderator: DANIEL A. MOROS, M.D.

Ian Holzman: I have a question for the philosophers. I wonder if anyone would like to suggest some philosophical underpinnings for something that has come up in the discussion. Why would it be argued that a small infant who may well prove to have multiple disabilities should not be given medical care? Why is it at all acceptable to say that a small infant is less worthy of medical care than someone else?

Peter C. Williams: I will give you a fairly straightforward answer, something physicians have to deal with all the time. There are two grounds for saying that, when it is said.

One is a claim not that the life is less worth living than anyone else's or that handicapped children are somehow less human or anything like that. It arises from an appraisal that the anguish, suffering, or lack of ability to have any sort of meaningful interaction or life is too great a burden, or that a future of pain and operations for a short period of life is insufficient to justify intervention. Someone who loves a child, like the parents, and someone who does not have that affective attachment but has medical expertise—the health care team—agree that treating this child is not in the child's best interest. That is ground one. You may think that set is empty, but that is a ground.

The second is that the treatment will not work. The particular child either has a concatenation of problems or a particular individual problem that cannot be fixed. The child is in the short run doomed, and so interventions between now and that death are pointless.

Question: But what about the period of time that the child is around? It appeared in the case presented that the child would only have a year but the child is now over two years of age.

Holzman: We said that this child might not make it, so we thought it was, at that point, okay to offer the parents the chance to opt out of any kind of heroic care.

Williams: The two grounds mentioned above exist. An answer to the question is, you try to do things for the benefit of the child, which you may be wrong about or you may be right about. Also, there is the consideration of medical futility, which you may be right or wrong about. Those are common grounds and they are accepted grounds in all the neonatal intensive care units I know about.

Andrew Jameton: First, I want to say something about a weakness in philosophy, taking up the case of the head injury in particular, the disappointing story of the young man in whom so much was invested yet whose life seems to be going so badly. I get this case or ones like it often around the medical center. Part of the problem is, I think, that philosophers really do not know much about what is real. A lot of things happen that, since philosophy has largely directed itself at how to make the best decision, philosophy does not have much to say about. All you can say is, "Gosh, that was terrible." But there is not a lot of philosophy around "gosh, that's terrible." That is, there are philosophies about suffering and about disappointment, and I think if we move more broadly into philosophy we can find some things that give us some sort of solace or comfort, or help to address our feelings of powerlessness, or answer questions about where to address our anger. I think that, in some ways, when we are talking about what the justification is for this kind of decision, we are not really talking about what needs to be addressed in these kinds of cases. You can hardly find anything justifiable or wonderful or good news in some of the really tragic stories.

Adapted from a panel discussion at the conference "What Do We Owe People with Disabilities?" at The Mount Sinai Medical Center on March 5, 1993. Address reprint requests to the moderator, Assoc. Prof., Dept. of Neurology, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1137, New York, NY 10029.

Williams: I have one other quick point: "Top Cop" is on television now, and "America's Most Wanted" is too. We could do "America's Most Needy." These stories are horrible stories. Actually, one turned out quite well, we hope. But the other case is unabashedly complex and horrible, and it is hard to know what a philosopher or social policymaker or physician can say when given a story like that and asked, "Yes, and now what?" It is hard to know what an answer to that would be.

Kristjan Ragnarsson: Yes, you are right about the man with the traumatic brain injury. When he was injured, and soon after, it looked a lot worse than it ultimately turned out. He was blind, he was totally confused, we could not deal with him, he could not walk, could not care for himself. Ultimately he was able to do all of those things, but he was still impulsive. Now this man was also totally dysfunctional before his injury. From my perspective, I do not think he is any more dysfunctional now than he was before. He was not a good bet to begin with, but we still have to provide people like this with services and help them the best way we can. We do not rate whether a person needs those services based on their past performance. I cannot see how we could or should do that.

Peter Caws: I would like to say a couple of things in response to the question that was just posed. It astonishes me that you ask us to give an answer to those questions. I have thought a lot about the concept of obligation. I do think it is important to think at the deepest level you can and at the most general level so as to see if you can get any kind of agreement that might be taught, and that might constitute a kind of common ground for the argument. Dr. Ragnarsson says we need to "build bridges" and, of course, he is right. Who could help being struck by the difference between the meditative reflections on the origins of the concept of obligation offered here on the one hand, and these very concrete cases on the other. The question is, how one builds those bridges. The thing that struck me about your question is that my response would be you include everybody in the moral community you possibly can, but you run up against practical limits. When that happens you cannot give an off-the-cuff answer or even a sort of principled answer. That is when you have to engage a lot of the particulars that I was talking about. And that does not happen until the conversation has gone on between philosophers—and more and more of them are in medical schools now—who actually have the chance to sit around with people who work in the intensive care unit and have some sense, when a case like this comes up, of which way to jump—what the alternatives are, and so on.

I think it is a bad idea to think of philosophy as being in a position to give answers to any question whatever. I think what philosophy can do is to help to lay a groundwork of common understanding of the most basic things that characterize humanity, the most basic things that characterize the enjoyment of life, what the meaning of life is. That is not a phrase I am in the habit of using, since I am not sure there is such a thing, but we can talk about what makes episodes of life meaningful, and we can try to discover how to optimize, when you get to the crunch of the real world, the resources there are. Part of the point, I think, of meetings like this is that nothing is really given. It really does require conceptual exploration and digging. It has to be done, and an important point is that this is the forum for it—not in the ICU when you are in the middle of a situation, and not at budget hearings. The forum for these discussions is when you can get people out of all that and into a situation where they can actually talk to one another and confront issues.

Question: If you consider how we are spending money on cases like these two and then think of Somalia, or South Africa—terrible situations—how can we justify spending so much money on so few people when that kind of money could save the lives of hundreds and hundreds of people? I think this is a real philosophical problem. I would make the problem a problem of method. There are niceties in our interpersonal relationships, and these are quite different from questions of policy. The policy maker has to make some general decisions which may deprive some people and which may be very tough on some people, or which may give some people new advantages. It is a game very different from making individual decisions in an ICU. We invest rather large amounts of money in our medical welfare and the welfare of professors of medicine to do some very fancy stuff. Perhaps we should be feeding some people or doing something for those of much lower wealth.

Holzman: I am not sure that anybody would disagree with you. The problem is, making decisions about the allocation of resources on the basis of the existence or potential existence of disabilities may not be an appropriate way to decide how the money is to be allocated. If you do not want us to spend the money, time, and effort on a potentially disabled or currently disabled baby, is it because he or she is going to be disabled that we ought to eliminate the spending of money on that person, or is there some greater reason not to care for a large segment of people, period? This comes up in

neonatology all the time. Should we be spending money on little babies who might be disabled? I am not sure that couching it in that way is appropriate, and that is part of why this conference is occurring.

Jameton: Surely, this is not a trade-off simply between NICUs and rehabilitation, but must be viewed as a larger trade-off in our other enterprises that make us wealthy or pose financial problems. In the state of Nebraska, there is a big attack on Medicaid; they want to save money by cutting back on it. But Medicaid costs have not increased as much as state payments for insurance for its state employees for health care.

There are two big puzzles. One is, if we are going to try to make a bigger pot, which I think would help us distribute resources better, then how would we go about setting up social relations to make those decisions? I think we would always have tremendous controversies. Another thing is that your case was very striking because although there were some highly paid professionals involved, there were a whole lot of low-paid people involved too. These costs begin to add up in terms of real costs of the numbers of persons involved, although perhaps nothing like, say, the number of people who were involved in my own education. I do not think that just by pointing out the wealthy, we really resolve this problem of resource allocation. The problem is to find out where to discuss it, who should be involved, and then how to go about having that discussion—it is a desperately difficult one.

Anita Silvers: I am going to change the subject. As the author of a casebook, I know that cases are not innocent. You choose a case in order to illustrate something or other. I would like to ask each of the gentlemen who selected a case, what made them choose the case? Then we can see whether the reason it was chosen had anything to do with the topic of this conference, or if it has to do with something else.

Joseph Stillo: I would love to respond to that. To respond to the earlier question, I think that there are a lot of other places you can get money to feed the kids in Somalia, like defense budgets—but not from monies for disabilities.

I chose this case because I was wondering if any of the things that I said would raise any questions in your mind. Did it matter that this was a 22-year-old guy who, as Dr. Ragnarsson said, was dysfunctional before his injury, had three kids, was never married, was a drug abuser, could not hold a job, was rejected from the U.S. Army, dropped out of school in the eighth or ninth grade—does it make a difference to you that this

is somebody that we choose to allocate a huge amount of resources to for rehabilitation? Consider the per diem rate for rehabilitation at Mount Sinai, plus what it took later on in Medicaid expenditures. Is that a way you want the money to be spent?

I discussed these problems with some friends and colleagues in the Rehabilitation Medicine Department before I chose this particular case because I could very easily have chosen a number of cases—for example, people with quadriplegia who have returned to their nursing duties or to Wall Street. But that is easy. I do not know that we have a problem with those. This is a case that a lot of people have problems with. Even within the Rehabilitation Medicine Department, it was difficult to treat somebody like this, especially when we often had difficulty separating out his premorbid personality from the result of his head injury—he was very volatile. This was somebody who had to have a one-to-one security guard. Because of his head injury, he wanted to bash people's faces in when he first got there.

Silvers: Would it make a difference to you if I told exactly the same story? In California enormous amounts of money are invested in the higher education of persons with a history something like this person's. They have been in jail, or they are in jail, and they can get a high school degree. We send professors up to teach them. We give them scholarships. Then they go back on drugs and kill somebody. Other people perhaps less colorful do not get scholarships. Is that the same story? Because if it is the same story, then the question is really about whether we want to invest the money in people with certain kinds of histories, regardless of what it is that we are investing in. For me it is the same story.

Daniel Moros: A comment that to some extent changes the nature of the discussion of this conference from medical treatment to a perhaps broader one. Walking through a part of the Department of Rehabilitation the other day, I thought that particular hallway was one of the saddest places I have seen, because in it a lot of young kids from the neighborhood, who were involved in crime and are now paraplegics or whatever, are sitting around, waiting for services. In a sense, these people in rehabilitation represent a sort of a double-whammy for our society because you could argue that in a way it is not their fault that they are in this situation. We do not know where these people come from or what their backgrounds are really like. Maybe it is in part the lack of education, lack of family support, lack of all those other things that we need to be supply-

ing in our society along with medical care. These people are perhaps twice victims because they come from terrible backgrounds and now they are confronting medical care costs and might worry about whether or not they are going to be provided for.

Question: I think that in any discussion about choosing not to help people because of their past history, you remove from them the possibility of personal rehabilitation. Not just in the sense of physical medicine and rehabilitation, but in the sense of changing one's life around. Many of the people who work as drug treatment counselors are themselves rehabilitated drug-abusers who are able to do it precisely because they understand the drug abuse experience. So, if one of them needed care, and we chose not to give it to him or her because of a past drug history, for example, we would essentially wipe out any hope of helping other people to cure the conditions that we are complaining about. I think that is the sort of reasoning that curls in on itself. People are capable of change, and I think that unless we judge on the favorable side, we get very quickly into thinking, why spend money on any program, because it is all futile.

Silvers: So you agree with me that whether it is education or whatever, these are general societal questions, not anything particular to the allocation of medical care.

Stillo: When we are screening patients for the in-patient rehab unit, we want to maximize the chances for success. We want to allocate the resources as best we can to maximize the chance for success. Regardless of a history of imprisonment, drug abuse, smoking, and so on, people must follow the laws of the hospital. We have had nurses who have had to be followed to the parking lot by security guards because their lives have been threatened. We struggle with many issues. How do we deal with people like this? We say we are all nice people here; however, I wish patients and families would unanimously support that. I do not think you are going to find that. You are going to find that we are prejudicial in the way we allocate resources. We are prejudicial in the way we staff our department. Sometimes we do not quite understand the patient and what the patient came from; there are many issues we struggle with. I would love for somebody to say, "Yes, you can admit that patient. No, you cannot admit that one." Unfortunately, we are in the position of making that decision. As long as the hospital says we can admit them financially, we will dispense the resources without any regard to all those other preexisting problems.

Bernard Baumrin: All you've said about the case of the head injury impressed me a great deal. I do not find that this discussion has yet got to where it could go. The burden of proof is on those who would offer to treat the person at all because those resources are being diverted from someone else. Given the way you have stated the case, it looks like a huge waste of effort. So what was your justification? Is it just that the money was laying around? In the absence of a philosophical principle, your justification of the allocation of resources to that individual at that time seems to me to be arbitrary.

Stillo: Off the top of my head I can ask you, would you rather this patient be transferred to a nursing home for 24-hour nursing home care for the rest of his life? I think the burden is on you to tell me that we wasted resources and that he would have been better off in a nursing home. The fact is, we reintegrated this person back into the community. This patient had a very involved mother. Perhaps the outcome should have been predictable, perhaps not. But the fact is that we got away with eight hours of attending care for seven days a week, got him back into the community on an outpatient program, until things turned around.

Baumrin: Are you suggesting that the justification is that in this way you were saving money and that the other way would cost more?

Stillo: No. Just addressing that financial aspect, that is all. If you want me to justify treatment on a financial basis, that is how I would justify it. If you want me to justify it humanely and ethically, I will say: because the gentleman was in need of our services.

Ragnarsson: I think there is a legal element here too. Can you deny prisoners care in the New York State penal system because they are going to be in prison for the rest of their lives? You cannot, as a matter of fact; they have to have the same services and the same accommodations as a disabled person living in the community. But I sympathize with the question because we as a society have to ask, "How is my investment in this person going to pay off? Is it going to grow or is it not?" The answer to that is that probably it is not as good an investment as putting it into somebody who is quadriplegic and has a job to go back to and can function independently with minimal support services. But we as physicians cannot make that distinction. We have no rating system to take a look at what the personal life of the newly disabled was before and whether they are worth spending money on. We cannot do that. Society would have to do that, not physicians.

Question: I think that what you did was a success, and I find it remarkable that there was ever any question about serving this individual. I think, though, that there were really two rehabilitations that needed to be addressed—a primary rehabilitation and a secondary rehabilitation. You dealt with a short-term rehabilitation—three months in rehabilitation seems remarkably short to me. But then you have the dysfunctional aspects. What he is now is what he was.

Baumrin: I want to know qua citizen, why we ought to divert resources to this bum, and unless you can justify that, then there are other places to direct those resources that are more beneficial. Unless you can tell me that, as a citizen I am reluctant to think that my tax money is being used properly since I cannot see the moral basis being used to justify such allocations of resources. With respect to the philosophers, they did not present a knock-down argument for taking resources for this purpose primarily. Yes, tangentially to be sure, in addition to other resources, pooled, surely. But not primarily.

Stillo: If you are asking that the allocation of medical resources be decided upon by the citizenry, as you referred to yourself, and not by physicians, my response is, Tell me how you are going to draw up the criteria? Who is the bum and who is going to get the resources? I do not know how else to respond to that. We need criteria from citizens. If you do not want physicians in the position of allocating resources, help us. You tell us who deserves rehabilitation, who deserves the resources and who does not. Because right now, we do not seem to know.

Caws: These sorts of discussions are difficult because they are multidimensional. I want to pick up on the issue of the two rehabilitations, which I think is very important. You will remember, though I did this in passing, as a joke, that in my paper I said, not only should there be a People with Disabilities Act, but there should be a People Who Went to Rotten Schools and Spent Too Much Time in Front of Television Act. I meant that to stand for all the things that make people what they are. If we want to take seriously the idea that we have a community in which people are free and equal, we need to make it possible for those things to be addressed. I do not mean for a minute that we should thrust anything down anybody's throat, just as, of course, the ADA does not.

The other thing that is running through here is Prof. Baumrin's remark about diverting resources, which was not addressed directly. I do not know what the situation was in your rehab unit when this chap came along, or whether or

not there was somebody else for whom you were going to do something expensive but decided not to because there was this new patient. I do not know if that kind of thing happens or not. While there are lots of cultural similarities, what the ADA and other such instruments have to do, sooner or later, is to draw something up that is going to function even when there are cultural dissimilarities, when people do not share the same emotional or sympathetic grounds. What is needed is to build a structure which is going to be multicultural, and I do not use that term in a PC sense. If we are filthy rich and it is a question of diverting resources, we are still pursuing a line where what gets divided is something like money or other resources that are necessarily diminished when they are divided. We are talking about a limited pot. How do you redesign the community so that the pot is big enough so as not to exclude anybody?

Rather than say, "No, we cannot spend the money here, we are going to spend it in Somalia," we might try to think of how we can optimize the distribution of goods which can be shared without being diminished—like knowledge for example. It is a good thing, it seems to me, to try to show a family how to look after a young child who is disabled. There are lots of ways in which we might make use of the resources we have got that are not dollar resources—resources of various abilities, sources of education. It is a question of redesigning the whole thing in a much broader way, not just the problem of looking after a particular class of disabled people.

Holzman: I chose this case because a part of me is not at all convinced that anything we did was correct, and many of the people who worked with this child over many months in our hospital felt that we had done wrong by this child and the family. I am the one who advocated not operating on him and not sending him to another city. I am perfectly happy doing less rather than more, but treatment still used an enormous amount of resources. As it was happening, as this child was staying in our unit, it seemed clear that he was going to be more and more disabled. People on staff were expressing the view that it was absurd to be continually bagging him. He was hypoxic, he was not getting enough oxygen, he was not growing, he was not developing. This is an inappropriate medical model for taking care of someone. Why were we doing any of this? There were major disagreements among the medical staff. The biggest disagreement came from the house staff, all of whom initially felt we should do everything. They thought the child should be put on

an airplane and sent to Cincinnati within minutes after arriving here, and I had to have an emergency meeting with all the house staff to dissuade them. The fact that we could do it did not mean we had to do it. Then it all shifted. All the house staff, three months later, were asking, "Why are we doing this?" They thought it was a big waste.

Silvers: This is really interesting because either you do something incredibly expensive, major intervention, or nothing—which in this case probably saved his life. Even if you are not doing anything that is very exotic, the problem is, you do not always know the outcome. Maybe this kid with all his disabilities is, because of his good throwing arm, going to throw knives into people, or maybe he will turn out to be incredibly productive. You cannot know, but you do not know about any 2-year-old. And that is the interesting thing.

But the fact that one cannot imagine what his life will be like does not matter. One of the things I do know is, if you are not used to a particular level of activity—I have not run on the beach for 43 years—you do not really miss it very much. If you are not used to it, and particularly for kids, you do not know that it is a great absence or lack in your life. You live perfectly happily without running on the beach. The issue is, is he going to have enough opportunity? Is he going to have enough to do? No one in this room has access and opportunity and ability and skills to do every single thing, to enjoy every single thing. All of us have some things we cannot do.

Holzman: Let me just ask you one question. Did his parents have the right, if you want to talk about rights, to decide initially that he should not get medical care? That came up—they were given all the options. Should the parents be able to decide, based on his disabilities or the burden of his disability to him, or to the family, or because of his medical condition, whether or not to treat him?

Silvers: But notice now, this is a more general question that our society is beginning to raise. What rights do parents have in general regarding children? We have thought at some times that children are property, whether able-bodied or disabled. We do not think that anymore. Now we have kids who say to their parents, "I am divorcing you." And some of them should. This has to do with what kinds of interactions and decisions parents should have with their children.

Question: It is of interest to me that initially the house staff was gung-ho to do every thing they could. Was it because at that point, in their minds that child could be restored to what we might con-

sider normal? To what extent was the disability not an issue until three months later?

Holzman: For the house staff, I think you are absolutely right. For the house staff initially, I think there was a fantasy—that is my own bias—that a treatment offering a cure could be given somewhere. Therefore the doctors wanted to attempt to ameliorate the medical problems. They did not see this as a disabilities issue, initially. When they did, they shifted totally around and said, "My God, look what we have done to this poor family, we have left them with a disabled child." Every day on sign out rounds they wanted to know whether they really had to bag, to try to resuscitate or not resuscitate, or what to do at night. They wondered whether these parents would be happier if we did not keep giving the baby medical care.

Silvers: Why should medical personnel think they are especially qualified to determine who is going to be happier? The medical personnel sometimes, I think, are miserable—they make themselves miserable. They shoulder the burdens of the world. They complain a lot. Why should they shift into making judgments about whether the parents would be happier or other people would be happier? Medical personnel are not experts on happiness. Thank God, philosophers are not either.

Holzman: But we get placed in that position by the families to make those decisions.

Silvers: I think you take that position! You know you have got families under stress, and instead of assisting families in making decisions under stress, you make the decisions for them. You are under the kind of pressure where decisions need to be made and so you make them. I think to turn around and say, "Society gives us this power of decision-making, so we will" is begging the question.

Moros: I have a question that relates to something that Professor Caws said earlier, and has also been reverberating in the discussion. When we talk about changes in our society and the recognition of new rights of the citizenry, we expand our views of people's right to medical care and perhaps the right to equal education and a variety of other rights. Have we recognized any new rights for the disabled? Or have we simply recognized the disabled as existing within our society? What really is the change that we are talking about here? The more we talk, the less certain I am that we have recognized any new rights for the disabled, and that we have just recognized people whom we have managed one way or another not to see so clearly in the past.

Caws: I think that it is a question of the long and progressive enlargement of this community I was talking about, and in the end, the ideal would be not to make subdivisions in the community, but to use the resources we have to make it as inclusive as possible, subject to conflicts of interest.

In general, not assuming that we know what it is like to live as another does is a very important thing. As Professor Silvers said, she does not miss running on the beach. For people who run on the beach to wonder what it would be like not to, or to say, "Gosh, how terrible it would be if I could not!"—that is the whole QALY problem in a way, because we are asking people who are well to say how much they would agree to give up. In the winter of 1947 I was a 16-year-old in England. It was the coldest winter there had ever been, there was no fuel, and it was postwar. I had to walk, pushing an old baby carriage, two miles in sub-zero weather, wearing a thin coat, getting chilblains, to get coke for the family fire. This story came up the other day and one of the people in the group had tears in her eyes. She said, "How terrible for you! Oh God!"—she was empathizing like mad! I said, "Not at all! I mean, it was cold, sure, but that is just what we had to do. We had just come through the blitz." It does not look the same when you are there. There are some circumstances under which it may look worse. My imagination might not be up to knowing what it is like to have my child charged as a criminal. That could be much worse than anything that has ever happened to me. But you cannot construct the society on the basis of a lot of a priori assumptions about the nature of the people in it. What you have to do is to make it as inclusive as possible.

I think Dr. Moros is right. These are not really new rights, but a new recognition that it is possible for us to allocate resources. I really think it is possible. I think it is possible even quantitatively. Even with all that there is to be dealt with, it does seem to me that we are probably in a position to deal with it if we really want to. For example, we could consider what we export and not try to stretch a finite resource but try to make self-reproducing resources. We could try to do more in terms of knowledge and so on—maybe even worldwide. What is necessary is that people be educated into the desire to do this. I think all the political work involved in getting something like the ADA passed in fact turns out to be very useful.

Question: Why the house staff made that "remarkable" switch mentioned earlier is not remarkable to me at all. Acute-care house staff are not trained in long-term care. I think perhaps

only in physical medicine and rehabilitation and perhaps psychiatry and among those of us who do primary care do physicians look at life as anything more than one discrete event leading to another. Short-term hospital care is very event-focused, as is Western society as a whole. It is much more of an Eastern philosophy to see life as a process. The experience of seeing the whole life in long-term care is not something that most residents receive.

So, in terms of decision-making for life events, in any setting, be it hospital or nursing home, I think it would be much better to access the medical ethics committee, which is composed of clergy, nurses, physicians, philosophers, a lay person from the community and administration, so that these decisions are not arrived at in a vacuum. Then nobody needs to either make the decision him or herself, or throw it on the family who is equally unprepared to make it. These should be reasoned decisions with a number of people who are not immediately involved in the situation. I think that is the way you get the best reasoning done and can fight through to the best result that you can hope for.

Ragnarsson: I think it is possible to put the problem of the allocation of resources for people with physical disabilities into perspective. I do not think that it is as big a problem compared with some of the others that we are dealing with in medicine today. There is, for example, the general problem of who has health insurance and how it is allocated. Secondly, with the technology available today, when should we use all of the technological means that we have in this hospital in the treatment of given individuals who are here? Thirdly, I will mention the problems associated with the aging population. How do we decide on the allocation of resources for the elderly? In some cases we know, statistically, that a given patient's life expectancy may not justify everything we are doing. Recently there have been a lot of papers on the issue—about intensive care management for people that everybody can tell do not have a very long way to go. I think the ethical issue of providing resources for people with physical disabilities is a relatively simple one compared with those three issues.

Whatever the former lifestyle of a person, to me there has never been a question whether everyone has a right to rehabilitation services and the help of society to get back to a level of functioning as similar as possible to what they had before, even if it turns out that it is not very high—as with the young man with the traumatic brain injury. But I think these folks have a right

to these services and we are obligated to provide them.

Question: I wonder if I could say something, as a disabled person. Thanks to all the progress in medicine in the last twenty or thirty years, doctors have gotten us to the point where we are able to get up and get around. I was initially told that I would never function independently and would have to live in a nursing home. I live alone with my two cats in an apartment. I do volunteer work here. Taxpayers' money has paid for all this. I came here representing an activist group. I came here ready to do battle, because we did not like your title, "What Do We Owe People with Disabilities?" You do not owe me a damn thing. I have the right to certain things. I do not want more than you, but I have the right to as much as you.

If you had said "What Do We Owe People," or "Do We Owe People with Disabilities Anything?" our group might not have objected. We were ready to picket this place with twenty or thirty wheelchairs. As Dr. Silvers said, you do not really know what it is like to be disabled. You think you have a good idea of what it is like because you see it day after day, but when you go home it is behind you. I go home and I take it with me. You do not really know. I did not before I was disabled.

I also believe in the ripple effect. I am working as a volunteer touching other people's lives. I can go to them and tell them things which a therapist or doctors can talk to them about, but I really know what it is like and we get together and we talk. I am part of the ripple effect. My life was worth saving.

Issues in Medical Ethics

2. Science and Alternative Care

Alternative Medicine and the Orthodox Canon

NORMAN GEVITZ, PH.D.

Terminology

MANY TERMS other than "alternative medicine" have been employed to describe the phenomena we are considering.

The Terms and Their Sociologic Uses. In my own writings I have used some of these expressions, notably "unorthodox medicine," "unconventional medicine," "marginal medicine," "complementary medicine," "irregular medicine," and "medical quackery." What all these terms have in common is that they denote some significant putative difference between the dominant and culturally sanctioned practice of medicine and other forms of health care practices and services.

Where these various terms diverge is in their connotations. On the one hand, little that is positive can be attributed to a practice or service that comes under the heading of "medical quackery"—a term historically used by the dominant group of Western practitioners since the 17th century to describe most, if not all, of their challengers. On the other hand, the term that these challengers have recently come up with to describe who they are and what they do—"complementary medicine"—connotes a benign and supportive practice or service that would appear to offer no threat to patients or for that matter to the dominant form of medicine. These two terms represent the extremes of popular characterizations; the others fall somewhere in between.

One of the strengths of the term "alternative medicine" is that it appears to describe the phenomena in a morally neutral way. It announces the subject as something that is different, but not necessarily right or wrong. We do not have to prejudge the phenomena. From the standpoint of the researcher looking into a form of "alternative medicine," this concept is valuable insofar as one should be open-minded when beginning one's inquiry and should not look for information that supports only a particular point of view. The term sounds politically correct, and the NIH was certainly acting wisely when it named its new division the "Office of Alternative Medicine."

But even though I use the expression "alternative medicine" a great deal in my own writings, and despite its virtues, the principal term I employ when describing this phenomena is "unorthodox medicine." The expression "alternative medicine" assumes that no necessary moral status attaches to a given practice or service; the term "unorthodox medicine" recognizes that historically and sociologically, sets of social statuses have been attached to given services and practices by the dominant group of practitioners and by the public. In fact, the behavior toward each other and the interaction of the dominant group of practitioners and their challengers is shaped by their respective reputes in the scientific and lay communities. From a sociological standpoint, it would be a mistake to consider the phenomena we are looking at as "only" different. Each form of "alternative medicine" has been considered by the dominant medical world and the public to be "deviant" in varying degrees. In my line of research it is important to understand why different forms of alternative medicine are considered deviant by orthodox medicine and most of the public, the ways practitioners of these unorthodox forms of medicine have adjusted to their status,

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and how they have attempted to rid themselves of the "deviant" label.

To be precise, for my purposes "unorthodox medicine" constitutes practices not accepted as correct, proper, or appropriate or not in conformity with the beliefs or standards of the dominant group of medical practitioners or lay persons in a society. Individual healers who persist in engaging in these activities in spite of the disapproval and opposition of members of the dominant group may be classified as "unorthodox practitioners." My use of the terms "orthodox practitioners" and "unorthodox practitioners" serves neither to condemn nor condone, but rather to organize the field and help explain the relationship between those who fall into one category and those who do not.

Orthodox physicians can be differentiated on the basis of education (low-grade, acceptable, or superior training), skills (minimal, ordinary, or extraordinary), and type of practice (generalists or specialists). The point is that, however they may be differentiated from each other, orthodox physicians as a collectivity share certain ways of apprehending phenomena and certain ways of diagnosing and handling problems and maintain certain standards of conduct—all of which binds them together. In short, they can be regarded as being part of a professional community in that they speak the same language, rely on the same general pool of knowledge, share certain beliefs, subscribe to similar values, and strive for common goals.

It is not possible to say the same thing for the general category of unorthodox medical practitioners. Although they can be differentiated according to training, skill, and type of practice, they do not constitute a distinct community. In fact, they represent a heterogeneous population promoting disparate beliefs and practices that vary considerably from one movement or tradition to another and form no consistent or complementary body of knowledge. I do not imply that there are no similarities or social, political, and intellectual ties among them. What I mean is that the only fundamental characteristic they share is their alienation from the dominant medical profession. As a whole, unorthodox medicine has no real corporate identity, although within each movement or tradition a great deal of consensus may be observed (1).

The Orthodox View: Historical Perspective

How has the dominant American medical profession viewed unorthodox medicine, how has

unorthodox medicine reacted, and why? When the medical profession in America sought to organize nationally in the middle of the nineteenth century, one of the top priorities of the leaders of this movement was to define who should be considered a "regular" versus a "nonregular" practitioner and, once having done so, to determine what actions regular physicians should take against those violating the canon of orthodox medicine. When the American Medical Association was formed in 1846, it quickly adopted a Code of Ethics, which contained a so-called "consultation clause." It declared, "No one can be considered a regular practitioner, or a fit associate in consultation, whose practice is based on an exclusive dogma, to the rejection of the accumulated experience of the profession, and of the aids actually furnished by anatomy, physiology, pathology, and organic chemistry" (2).

Worthington Hooker. The most articulate spokesman for the AMA Code was a Connecticut physician, Worthington Hooker, whose *Physician and Patient*, first published in 1849, was the first systematic treatise on medical ethics by an American. Much of his book is concerned with sectarian practitioners (3).

Sectarian medicine constitutes but one form of unorthodox practice, consisting of individuals who band together around a set of deviant health beliefs, establishing their own medical schools, journals, associations, and hospitals. In America, the most prominent examples have been homeopathy, eclecticism, Thomsonism, and physio-medicalism, which flourished in the nineteenth century, and osteopathy and chiropractic, which have flourished in the twentieth century (4).

Against these sectarians, Hooker gave five major reasons for supporting the AMA code "consultation clause"—themes recurrently expressed by advocates of that clause throughout the nineteenth and into the twentieth century. Hooker argued, first, that the belief system of sectarian healers was alien to the accumulated experience of the profession; second, that their practices were dangerous to their patients; third, that their education was inferior to that of regular practitioners; fourth, that their social behavior did not conform to that expected of gentlemen; and fifth, that any association with these healers both legitimized the irregular and lowered the status of the regular profession before the public.

Dangers of Unorthodox Medicine. Hooker's second objection—the dangers associated with unorthodox medicine, the "public menace" issue—appears to be the most compelling rationale for the AMA's subsequent actions against

unorthodox forms of practice. Hooker noted that "scientific" medicine was based on observation and experience. To understand disease, one needs to carefully record symptoms, determine the cause of the problem by gathering as much reliable evidence as possible, weigh variations and circumstances peculiar to the individual patient, and consider all relevant factors in the case before deciding on therapy. With respect to medicinal treatment, the type and content of intervention should be based on the known and predictable physiologic effects of the dosages of the drugs employed.

Sectarians, he argued, framed their whole approach to disease on theory rather than observation. They were rationalists who took a few observations and expanded these findings into an all-encompassing system to explain all the problems in disease causation, diagnosis, and therapy. For example, Samuel Thomson (1769–1843) launched the Thomsonian movement on the belief that all disease was due to "obstructed perspiration," and that heat had to be restored to the body. Under his logic, all therapy was directed at opening the pores (5). Samuel Hahnemann (1755–1843), the founder of homeopathy, believed that all patients should be treated with infinitesimal doses of medicines that would closely mimic the effects of actual diseases and somehow substitute for them. He argued that a drug that would produce symptoms in a well person would cure those same symptoms in a person when sick, and that the smaller the dose the more powerful the medicine. He also maintained that almost all chronic diseases were produced by "Psora" or "the itch" (6).

In response, Hooker argued that such dogmas were the antithesis of scientific thinking. He asked how an "ethical" physician could associate himself with one who subscribed to these exclusive and ridiculous notions. Similarly, if Thomsonism and homeopathy were based on unscientific thinking, practitioners who blindly embraced these systems posed an obvious danger to their patients by subjecting the sick to a theory that went against the accumulated knowledge of the regular profession. Furthermore, the distinctive therapies these sectarians utilized posed grave risks. Hooker noted that the regimen of Samuel Thomson and his followers, puking and sweating all patients, caused needless suffering and death. As for the homeopaths, although the infinitesimal doses of their drugs did not physiologically do damage to their patients, they nevertheless did no good and prevented the sick from receiving remedies that had value.

AMA Enforcement of the Consultation Clause. By the mid 1850s, the AMA began to enforce its consultation clause and marshalled its forces against its challengers. All affiliated local and state societies were required by the national body to adopt the entire code in their own constitutions, and some began to hold trials and remove from membership physicians who were engaging in irregular practices or consulting with unorthodox practitioners. In addition, regular medical societies used the consultation clause as the basis for actively opposing staff privileges at hospitals supported by public funds for sectarian practitioners, blocking sectarians' service on boards of public health, and preventing unorthodox doctors from becoming military physicians and surgeons. In the minds of orthodox physicians, all these efforts were consistent with the overarching goal of "protecting the public's health," and these physicians proceeded to garner significant public support (7).

Response from the Unorthodox

Unsurprisingly, unorthodox practitioners had a different view of the motives of the supporters of the AMA code. They postulated three reasons for the AMA opposition: first, unorthodox practitioners were getting better results than orthodox physicians, making orthodox physicians look bad; second, orthodox physicians were themselves dogmatic in their commitment to their own system, which resulted in their branding everything they did not believe in as "quackery"; third, orthodox physicians wanted to restrict economic competition.

Although I am sympathetic in the main to the regulars' critique of unorthodoxy, it is clear to me that from a historical perspective, these countercharges by the irregulars were not without validity. At the time the AMA consultation clause was adopted, many orthodox physicians were still practicing what was called "heroic medicine," which included copiously bleeding all their patients in so-called "inflammatory diseases." Calomel, a form of mercury and a powerful cathartic, was known as the "Samson of the materia medica" and was used often because a standard orthodox procedure in most diseases was to "clean out" the body. Unfortunately, mercury is not readily excreted from the body, and many Americans of the era suffered over time the cumulative systemic effects of mercury poisoning, including the rotting of bones and the loss of teeth. Even after the Civil War, when orthodox medicine turned away from depletive therapeutics to drugs given

to "strengthen" the system, the widespread professional use of alcohol and narcotics meant that orthodox medicine continued, on occasion, to pose significant dangers to the recovery of their patients (8).

Homeopathy, the chief competitor of orthodox medicine during this era, counseled that the patient had merely to suffer the disease, rather than the combination of the illness and the means used to treat the illness. Consequently, homeopathic and other sectarian healers' claims of better results appear, in retrospect, to have had a basis in fact, independent of the validity of the philosophic and scientific arguments used to justify their therapeutic management.

Outcomes vs. Scientific Boundaries. Indeed, my study of the careers of certain forms of sectarian medicine in the 19th and 20th centuries led me to the general and perhaps all-too-obvious conclusion that even if orthodox medical practice was or is more scientific than any of its unorthodox competitors, this fact alone does not necessarily result in a more efficacious or satisfactory outcome with respect to the illness or problem presented.

Improvement by Cooptation. Furthermore, unorthodox medicine, whatever real dangers it has posed to patients either in the therapy itself or in causing a delay or omitting useful orthodox treatment, has nonetheless in some instances had a salutary effect on the practice of medicine. There is considerable historical evidence that unorthodox medicine helped stimulate public and professional interest in therapies and health concerns that once attracted little attention but were ultimately incorporated into orthodox medicine as part of its domain. For example, a number of homeopathic and eclectic drugs were integrated into the orthodox materia medica, and some magnetic healing methods such as hypnosis gained legitimacy and furthered mind-body research. In addition to empowering women, elements of hydropathy were transformed into the more respectable hydrotherapy. The popular health movements of the 19th century, and latter naturopathy, did—despite their extravagances—stimulate greater interest in dietetics and poisons in the environment. Recently, spinal and joint manipulation as furthered by osteopathy and chiropractic have achieved recognition by M.D. physicians. These unorthodox systems, though unappreciated by regular physicians and all vehemently attacked by them, have left an enduring legacy in the history of medicine (9).

Assessing the Controversy

The Economic Motive. Does this mean, as unorthodox practitioners have claimed, that orthodox medicine was primarily motivated by economic reasons for opposing its competition? I don't believe so. The AMA has historically viewed itself as both the voice of American medicine and the public's guardian in medical matters and has taken these roles quite seriously. In establishing and enforcing the consultation clause, the AMA does appear to have been motivated by its concern for the welfare of patients. Taking a strong stand against the "deviant" beliefs and practices of sectarian healers, the AMA sought to isolate those it truly believed were incompetent or inferior. Although the restriction of competition may have been a natural consequence of its actions, the AMA did not act in order to restrict economic competition. Furthermore, orthodox medicine has seen no distinction between its own interest and the public's interest in joining and at times leading the fight against patent medicines, strange electrical medical devices, and odd cancer cures, as well as fighting unorthodox practitioners on such issues as compulsory vaccinations, fluoridation of the water supply, and creation of what became the Food and Drug Administration.

With the scientific advances furthered and adopted by orthodox medicine in the late 19th and 20th centuries, the AMA and other voices of orthodox medicine can be understandably proud of the accomplishments of their profession. It is also understandable, indeed predictable, that they will continue to see dangers to the public in the practices of those who do not subscribe to the orthodox canon. Similarly, they will seek, where possible, to prevent the legitimizing of unorthodox practices and their proponents, as in orthodox opposition to the creation of the NIH Office of Alternative Medicine or to the inclusion of alternative health practices and practitioners in government and private health care plans.

But orthodox medicine has not been, and is not now, the only provider of health care services. Today, perhaps 60 million Americans depend on alternative practitioners for some aspect of their health care, and it is doubtful that the voice of orthodox medicine can be the only voice to which policy makers will or should listen in arriving at decisions that reflect the wishes of patients (10). One can hope, though, that more than simply raising their voices, those supporting the positions of both orthodox and unorthodox medicine can appreciate and learn from each other. As I have found in my own research, advocates of

orthodox and of unorthodox medicine have each often produced excellent insights into the shortcomings of the other, yet have utterly failed to appreciate the other's strengths.

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Evidence and Alternative Medicine

DOUGLAS F. STALKER, PH.D.

WHAT IS CALLED ALTERNATIVE or unconventional or unorthodox or complementary medicine is a ragbag of therapies, diagnostic procedures, and preventive recommendations. A look into these therapies, diagnostic procedures, and preventive recommendations discloses that virtually all of them have obvious evidence problems. This should come as no surprise because evidence problems have been a common feature—indeed, almost a defining feature—of alternative medicine. The National Institutes of Health Office of Alternative Medicine notes this fact in its statement defining alternative medicine (1). The statement cites three features that often appear in attempts to define alternative medical practices and interventions: they lack “sufficient documentation in the United States for safety and effectiveness against specific diseases and conditions,” they are not “generally taught in U.S. medical schools,” and they are not “generally reimbursable by health insurance providers.” The first feature—the lack of sufficient evidence—is the most important because it explains, in large part, why alternative practices and interventions are not generally taught at places like the Mount Sinai School of Medicine and why they are not generally covered by major health insurance carriers.

Three Evidence Questions on Therapies. When it comes to alternative medicine, the main topic has always been therapies or forms of treatment. The NIH Office of Alternative Medicine also takes this as its main topic or concern. The Office of Alternative Medicine has a congressional mandate “to facilitate the evaluation of alternative medical treatment modalities” (1), and the

Office itself states that its main goal “is to evaluate alternative or unconventional medical treatments” (2). In 1993 the Office awarded a total of \$880,544 in research funds to evaluate, among others, prayer as a treatment for substance abuse, acupuncture as a treatment for unipolar depression, ayurvedic herbal preparations as a treatment for Parkinson’s disease, and biofeedback as a treatment for diabetes. The Office has also sponsored conferences on “the collection of research data relevant to cancer” and “research assumptions in alternative medical systems,” among other topics. These activities—sponsoring research on alternative therapies and discussing how to conduct such research—do not address the most important evidence problem surrounding alternative medicine. Indeed, the Office of Alternative Medicine has a virtual congressional mandate to sidestep this problem.

There are three basic evidence questions to consider in connection with any therapy, alternative or otherwise:

- One: How much evidence should we obtain?
- Two: How should we obtain the evidence?
- Three: Should we obtain any evidence at all?

It is plain what we want in the way of evidence here. We want direct, experimental evidence as opposed to indirect, nonexperimental evidence. That is, we want evidence about how the therapy works in people, as opposed to evidence about how it works in a test tube or in an animal model, and we want evidence from a therapeutic trial (of one sort or another) as opposed to an observational case control or cohort study. In this context, obtaining evidence means running an experiment with people.

These evidence questions are not equally important. The real question about evidence and alternative medicine is question three, which is about whether we ought to collect evidence in the

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first place—whether, that is, we should test a therapy or not. Questions one and two are merely academic without a “Yes” answer to question three. The Office of Alternative Medicine has been dealing with evidence questions one and two by funding actual tests of therapies and running conferences on how to conduct these tests. The Office has not been dealing head-on with evidence question three, and does not have to deal in any serious fashion with it because the Office was created by people in the Congress who steadfastly believe that we should obtain evidence about the efficacy of alternative therapies.

Choosing Therapies to Test

Which therapies (that is, hypotheses) should we actually test in a clinical trial format? One view is that we should test all possible hypotheses in order to determine which are true and which are false. Since the alternative-therapy hypotheses are possible hypotheses, we should test them along with the other possible hypotheses. This view is obviously wrong. We can't test all possible hypotheses because there are too many possible hypotheses and too little of everything we need to test them: investigators, patients, medical facilities, materials, apparatus, time, and money. Smalheiser and Philipson, writing in the *New England Journal of Medicine* in 1984, overlook these facts when they claim that the “job of science” is to “disprove crazy ideas” and that “when scientists choose to ignore crazy ideas, we encounter tragedies” (3). They contend that “if we do not bother to test, for example, whether an extract of apricots (Laetrile) can cure cancer, we run the risk of repeating the error of those who refused to consider that an extract of limes could cure scurvy.” Smalheiser and Philipson want to test both the improbable and the probable hypotheses—which is to say that they want to test all possible hypotheses, in order to eliminate the risk of missing a true and important therapeutic hypothesis.

In the real world of medical science we must choose which hypotheses to pursue and which to ignore, and we cannot guarantee that our choices will always be the right ones. Although we may reduce the risk of making a wrong choice, we cannot eliminate it. The main factor in these decisions is plain enough: estimates of the chances that a hypothesis is true. If we have a list of twenty hypotheses for chemotherapy drugs for non-small-cell lung cancer and we must choose which hypotheses (if any) to pursue in a clinical trial and which to ignore, we will proceed by es-

timating the chances that each drug will produce a response rate of at least 20% in patients with non-small-cell lung cancer. We will proceed, in other words, by estimating the chances that each hypothesis is true, and make our choices based largely (if not wholly) by ranking the twenty hypotheses in terms of our estimates here. These estimates are estimates of the prior probabilities of our twenty hypotheses; that is, they are estimates of the probability that each hypothesis is true before it is actually tested. They summarize a heterogeneous collection of background information or knowledge that bears on the truth of each hypothesis, and they can be expressed in the form of a conditional probability statement such as $\Pr(H/B)$, where “H” stands for a specific hypothesis, “B” stands for a collection of background information or knowledge, and the entire expression refers to the probability of that hypothesis being true given certain background information or knowledge.

Probabilistic Independence and Dependence. If a piece of background information or knowledge is relevant to the truth of a hypothesis, it changes the probability of that hypothesis. If a piece of background information or knowledge is not relevant to the truth of the hypothesis, it does not change the probability of the hypothesis. This distinction can be expressed in terms of the distinction between probabilistic independence and dependence. When a piece of background information I is irrelevant to the truth of a hypothesis H, then $\Pr(H/I) = \Pr(H)$. When a piece of background information I is relevant to the truth of a hypothesis H, then $\Pr(H/I) \neq \Pr(H)$. Thus, relevant information either increases or decreases the probability that the hypothesis is true, whereas irrelevant information does not change the probability one way or the other.

For example, consider the hypothesis that topotecan is an effective chemotherapy drug for patients with advanced solid tumors, the piece of information that topotecan inhibits the formation of a nuclear enzyme needed for DNA replication and transcription (4), and the piece of information that topotecan is a chemotherapy drug with a four-syllable name. The first piece of information is relevant to the topotecan hypothesis because many of our effective chemotherapy drugs prevent cell division by interfering with the synthesis of DNA or its precursors. The second piece of information is irrelevant to the topotecan hypothesis because there is no connection between syllabic prosody and cell kinetics. Thus the inhibitor information increases the probability of the hypothesis, whereas the syllable information does

not change the probability of the topotecan hypothesis one way or the other. If, contrary to fact, topotecan had been inactive in vitro against a good number of murine leukemias and transplantable solid tumors, this piece of information would have been relevant, and it would have decreased the probability of the topotecan hypothesis because there is a connection between anti-tumor activity in vitro against animal tumor systems and antitumor activity against human cancers.

Testing Alternative Therapies

Left to its own devices, conventional medicine typically ignores alternative therapies instead of testing them in a clinical trial format. This fact shows up in the standard medical literature. If we survey issues of the regular medical journals in the Mount Sinai Medical Center medical library—journals such as the *American Journal of Medicine*, as opposed to journals such as the *American Journal of Acupuncture*—we will not find many articles about alternative therapies, let alone articles reporting clinical trials of alternative-therapy hypotheses.

A Medline search will easily confirm this. For example, Medline lists 2,798 articles (of one sort or another) as appearing in the journal *Pediatrics* from January 1989 through October 1994. Medline also indicates that none of these articles are about two of the most popular alternative therapies, acupuncture and chiropractic. It indicates that just one of these articles is about another popular alternative therapy, homeopathy. Indeed, this article reports a randomized, double-blind clinical trial of homeopathic medicine for acute childhood diarrhea (5). The trial was conducted in Nicaragua and it was funded by companies that make homeopathic medicines. In all probability, the journal *Pediatrics* has never published an article like this before.

The NIH Office of Alternative Medicine was created in order to “facilitate the evaluation of alternative medical treatment modalities.” This is an indirect way of saying that the Office was created because some people in Congress thought alternative medical therapies were not being tested as often as they should be in the regular medical community. This is a standard belief among proponents of alternative medicine. As they see it, many alternative therapeutic hypotheses have as much scientific merit as conventional therapeutic hypotheses which end up being tested in clinical trials and reported in mainline journals. Alternative medicine proponents invari-

ably believe that alternative hypotheses are being ignored for social, political, economic, and psychological reasons. For example, one member of the advisory board of the NIH Office, science writer Ralph Moss, believes that “the cancer establishment” has not supported clinical trials of various dietary and nutritional therapies either because these therapies cannot be patented or because they are so inexpensive to manufacture and sell (6).

How many alternative-therapy hypotheses have as much scientific merit as the typical conventional-therapy hypotheses selected for testing in a clinical trial format? This is a question about the prior probabilities of hypotheses. It amounts to asking how many alternative-therapy hypotheses have prior probabilities equal to or greater than the prior probabilities of competing, conventional-therapy hypotheses that end up in clinical trials. Hypotheses are competing hypotheses if they appear in the same list of possible hypotheses about a specific outcome for a specific disease: for example, a list of therapeutic hypotheses for relapsing-remitting multiple sclerosis that target the relapse rate.

There are a number of straightforward reasons—basic science reasons, source reasons, and methodologic reasons—for thinking that when we rank conventional and alternative competing hypotheses according to estimates of their prior probabilities (or simply provide a relative ranking of such estimates), the alternative hypotheses will be at the bottom of the list. Sometimes when we estimate the prior probability of an alternative hypothesis—indeed a popular one—the estimate is so low that we can regard it as zero for all practical purposes. Moreover, there are straightforward problems with one type of background information that proponents of alternative therapies typically emphasize: information about positive cases.

Basic Science Reasons for Prior Probability Ranking

Information from the basic sciences is invariably part of the relevant background information for a therapy hypothesis. This information typically provides the scientific rationale for a therapy hypothesis, especially by outlining a plausible mechanism of action for the therapy. Given one theory about the pathogenesis of a disease, certain forms of therapy will seem reasonable because they agree with the theory, or follow from it, or fit in with it, or might play a role in it. Given another theory about the pathogenesis of the dis-

ease, other forms of therapy may seem reasonable. This sort of connection can obviously change the prior probability of a therapeutic hypothesis.

Agreement with a Supported Theory. If a therapeutic hypothesis agrees with a theory that has a good deal of support, that agreement is a good reason for assigning the hypothesis at least a moderately high prior probability. If a therapeutic hypothesis agrees with a theory that does not have a good deal of support, the absence of support is a good reason for assigning the hypothesis a low prior probability. Many alternative-therapy hypotheses agree with theories that do not have a good deal of real scientific support.

The Immune Surveillance Theory of Cancer. Consider, for example, the late Lawrence Burton's immunoaugmentative hypothesis for treating cancer: that injections of his four serum proteins constitute an effective cancer therapy (7). Burton believed in a version of the immune surveillance theory of cancer. On that theory, if a person has a normally functioning immune system, their immune system will identify and destroy cancer cells; if a person has a weakened or suppressed immune system, their immune system will not perform this surveillance function, and any cancer cells will multiply. Burton claimed that his four serum proteins play important roles in this surveillance system, and that a person's surveillance system does not function properly unless these four proteins are present in the right proportions. On Burton's hypothesis, cancer patients do not have the right proportions of these four serum proteins and so we must adjust the proportions by injection.

However, if the immune surveillance theory is not well supported, Burton's immunoaugmentative therapy does not make much sense to begin with, which is to say that his therapeutic hypothesis should receive a low prior probability. Saul Green, a former professor of biochemistry and research scientist at Memorial Sloan-Kettering, discusses the status of the immune surveillance theory in a recent critical review of the basic science behind Burton's immunoaugmentative therapy (8). Green maintains that "there is strong scientific evidence that the unprovoked, normal immune system does not recognize and destroy cancer cells that arise spontaneously." Indeed, he maintains that by the time Burton was offering his therapy at a clinic in the Bahamas in the late 1970s, "a great deal of solid experimental evidence cast serious doubt on the concept of an immune surveillance against cancer in humans." If Green is correct on the status of the immune surveillance theory, it is a theory that has little

support and, for that reason alone, we should assign a low prior probability to Burton's hypothesis.

Low prior probabilities should also be assigned to a number of other hypotheses that depend on the immune surveillance theory, such as Carl Simonton's hypothesis that a program of psychological techniques (notably visualizing) is part of an effective treatment program, or might itself be an effective treatment program, for cancer (9). Simonton presents a "mind/body model" of how cancer develops and a "mind/body model" of how cancer should be treated. In his models, the immune system functions to identify and destroy any cancer cells, and some psychological factors (stress, for example) can suppress a person's immune system while other psychological factors (positive beliefs, for example) can stimulate it. Simonton adopted his "mind/body model" in the late 1970s and has continued to base his psychological therapy hypothesis on his version of the immune surveillance theory. The NIH Office of Alternative Medicine has funded a study of "imagery and relaxation" techniques for breast cancer patients; "imagery" is another name for visualizing.

Logical Compatibility with Established Information. There is another important way in which basic science information can bear—sometimes decisively—on the prior probability of a hypothesis: the hypothesis might be logically incompatible with a well-established piece of basic science information (10). Since the two cannot be true at the same time, we can estimate the prior probability of the hypothesis by using the complement theorem of the probability calculus: that $\Pr(\text{Not } H) = 1 - \Pr(H)$, where "H" stands for the well-established piece of basic science and "Not H" includes the therapeutic hypothesis in question. Thus the prior probability of the therapeutic hypothesis will be no more than $1 - \Pr(H)$. If the probability of the well-established piece of science is for all practical purposes equal to or exceedingly close to 1, the prior probability of the therapeutic hypothesis will be either 0 (for all practical purposes) or vanishingly small (at best).

Cranial Osteopathy and Fusion of Skull Bones. Consider a well-established piece of basic anatomy: that the eight skull bones of the human cranium are fused together by two years of age, and so at that point the eight bones cannot move unless, in effect, the cranium breaks. Experts in human anatomy (such as Edmund Crelin of the Yale University School of Medicine) will say without hesitation that this is indeed and without question an anatomic fact, indicating that experts in anatomy regard this piece of anatomic information as certain and thus as having a

probability equal to 1. Cranial osteopathy is a form of therapy that has been promoted for, among other things, learning disabilities such as dyslexia and dental problems such as gingivitis. Cranial therapy involves the eight bones of the cranium and the notion that they can produce a variety of medical problems when they move out of alignment. The right therapy for these problems, then, consists of gentle manual manipulation to move the bones back into alignment.

As a therapeutic hypothesis, this is logically incompatible with the certain anatomic fact; either the bones of the cranium move, and so cranial therapists can move them when they administer their therapy, or the bones (after age two) do not and cannot move as a result of gentle manual manipulation. Since the relevant anatomic information here is regarded as certainly true by anatomic experts, the prior probability of the cranial therapy hypothesis is for all practical purposes 0.

Homeopathy and Avogadro's Number. Homeopathic therapies have a similar problem with at least one piece of well-established information from chemistry, Avogadro's number—the number of molecules in one mole of any substance—a physical constant that any sober chemist views as beyond question. To put this another way, chemists take the probability of the Avogadro hypothesis as equal to 1 for all practical purposes.

The problem lies in how homeopathic medicines are prepared: by successively diluting the active substance. For example, we may take one part of the active substance (perhaps an extract from a plant) and dilute this in 100 parts of a water and alcohol solution, then take one part of that diluted solution and dilute it yet again in 100 parts of water and alcohol solution, and so on perhaps 10, 20, 30, even 200 times. In homeopathy, this process is called potentization, and it is supposed to produce a more or less potent medicine. The homeopathic claim is that the more dilutions we prepare, the more potent the resulting medicine.

Yet this process can easily produce medicines that have been diluted past the Avogadro point for molar solutions. There is, in all probability, not even a molecule of the active substance in these dilutions, yet they are supposed to be exceedingly potent. For example, this process can produce dilutions such that $\text{Pr}(\text{a liter of the dilution contains one molecule of the active substance}) = 1^{-38}$. Most doses of this dilution will simply be the solvent itself, but these doses are supposed to be very potent. The unvarnished homeopathic claim is, in effect, that nothing does

something; the standard chemistry claim is, in effect, that nothing does nothing. We can't have our chemistry and homeopathy, too. Since the Avogadro hypothesis is certainly true, the prior probability of typical homeopathic therapy hypotheses is 0.

There is nothing sophisticated about this problem with Avogadro's number for molar solutions. Most proponents of homeopathy know about this problem and acknowledge it regularly when they publish clinical trials of homeopathic therapies. For example, Jacobs refers to this problem in her article that reports a clinical trial of homeopathic medicines for acute childhood diarrhea (5). She characterizes the problem as a problem about having a scientific explanation for the mechanism of action of homeopathic medicines. Of course Jacobs knows that we do not have an explanation, but she nonetheless believes that we should conduct clinical trials of homeopathic medicines because of "the numerous anecdotal reports of its efficacy and its use by millions of people worldwide."

Clinical Trials and Bayes' Theorem. What can such trials ever prove? For instance, suppose the prior probability of typical homeopathic therapy hypotheses is 0, yet we conduct a hundred randomized, double-blind clinical trials of these hypotheses, and they all have positive results. Given this evidence, the probability of the homeopathic hypotheses is still 0. We can show this by using another simple theorem of the probability calculus, Bayes' theorem. We can state Bayes' theorem as $\text{Pr}(H/E) = \text{Pr}(H)\text{Pr}(E/H)/\text{Pr}(E)$, where "H" stands for a homeopathic hypothesis and "E" stands for the positive evidence from a clinical trial. This theorem tells us that the after-trial probability of the hypothesis is a function of three things: the prior probability of the hypothesis, the probability of the clinical trial evidence, and the probability of that evidence if the hypothesis is true. It is obvious what happens in this formula when the prior probability of the hypothesis, $\text{Pr}(H)$, is equal to zero. The hypothesis in question does not receive any confirmation from the positive test results. Indeed, the hypothesis in question does not receive, for all intents and purposes, any real confirmation from the positive test results even if we assign a vanishingly small prior probability to the hypothesis. Nonetheless the NIH has funded a study of homeopathic therapy for mild brain injury.

Source Reasons for Prior Probability Ranking

A hypothesis does not come out of thin air. Someone comes up with it, develops it, and pro-

motes it. These circumstances are relevant to estimating the chances that the hypothesis is true (10).

Jason Winters and the Tribalene Hypothesis. Consider an obvious case, the tribalene hypothesis, and certain facts about its chief proponent, Jason Winters. In his book *Killing Cancer*, Jason Winters claims that tribalene herbal capsules are an effective treatment for cancer (11). Winters discovered tribalene during his world travels and continues to be its chief proponent, believing that it cured his own brain tumor. Who is Jason Winters? The book cover tells us that Jason Winters has crossed the Canadian Rockies in a balloon, navigated a canoe down the great Mackenzie River, hunted polar bears in Alaska and kangaroos in Australia, tested safety belts by crashing Jaguars, appeared as Geronimo in the movie "Apache Agent," and worked as a stunt man in every film by Audie Murphy. Jason Winters is a colorful person and, given his background, probably an engaging raconteur. However, what is the probability that tribalene is really an antineoplastic agent, given that a person like this discovered it during his world travels? The probability is extremely small—indeed, vanishingly small.

Bernie Siegel and the Psychotherapy Hypothesis. Consider a less obvious case, the Siegel psychotherapy hypothesis. In his book *Love, Medicine & Miracles*, Bernie Siegel promotes his psychotherapeutic approach to cancer as an effective treatment (12). Although he did not discover this approach, he has developed the hypothesis along his own lines and continues to be its chief proponent. The book's endnote tells us that Dr. Siegel is a graduate of Cornell University Medical College, that he was trained in surgery at the Children's Hospital of Pittsburgh and the Yale New Haven Hospital, and that he is a pediatric and general surgeon in practice in New Haven, Connecticut. Although this background information is relevant to Siegel's psychotherapeutic hypothesis and changes the probability that the hypothesis is true—presumably increasing it to some extent—this is not the only background information that we need to consider here.

There is Siegel's 225-page book. Since he prefers to write popular books instead of professional journal articles on how to treat cancer, we must judge the caliber of his thinking about the topic by judging this book. One way to judge the book is to record the number of errors it contains. There are errors on almost every page of the book, and those errors are not sophisticated ones (13). For

example, he presents speculation as fact, equivocates on key terms, commits the fallacy of *post hoc ergo propter hoc* and of arguing from supporting data only, misinterprets published studies, demonstrates a one-sided reference bias, resorts to argument by innuendo, presents false dilemmas and false analogies, makes fallacious appeals to expertise, demonstrates ignorance of the history and methods of psychodiagnosis, claims to know things that no one can know, fails to make necessary causal distinctions, uses question-begging definitions, displays outright confusion over key notions, makes inconsistent claims, makes claims characteristic of pseudosciences, and cites obviously flawed studies as being otherwise. Given the number of errors and their type, what is the probability that Siegel's psychotherapeutic hypothesis is true? Exceedingly low. The pattern of error simply undercuts the information about medical education and training.

Likelihood. Some pieces of background knowledge are more informative or diagnostic than others and so provide a stronger reason for changing a prior probability figure. For example, the background knowledge about the caliber of Dr. Siegel's book is more informative or diagnostic than the background knowledge about his medical education and training. These points can be expressed in terms of likelihood ratios, which are a standard measure of informativeness or diagnosticity. A likelihood is a conditional probability statement about the probability of observing a piece of information (or datum) given that a certain hypothesis is true. We can express this as $\Pr(I/H)$ for a piece of information I and a hypothesis H . We can also speak about the probability of observing a piece of information (or datum) given that our hypothesis is not true, and we can express this as $\Pr(I/\text{Not-}H)$. A standard likelihood ratio involves these two likelihoods and can be expressed as $\Pr(I/H)/\Pr(I/\text{Not-}H)$. If this ratio is equal to 1, the piece of information I is not diagnostic; if this ratio is greater than or less than 1, the piece of information is diagnostic as far as distinguishing hypotheses H and $\text{Not-}H$ from each other. When the ratio is greater than 1, it favors hypothesis H ; when the ratio is less than 1, it favors hypothesis $\text{Not-}H$. We can measure the degree of informativeness or diagnosticity by how much the ratio differs from 1.

Likelihood in the Tribalene Case. The tribalene case is so obvious because of how far the likelihood ratio differs from 1. One of the likelihoods is the probability that an outdoorsman (or, more generally, a nonscientist) is the source of

tribalene given that tribalene is indeed an effective cancer therapy; the other likelihood is the probability that an outdoorsman (or nonscientist) is the source of tribalene given that tribalene is not an effective cancer therapy. We do not need to worry about coming up with estimated numbers here because it is plain that the first likelihood figure will be many times smaller than the second likelihood figure—perhaps many orders of magnitude smaller—and so the ratio will be much less than 1 and the datum here, that the source is an adventurer (or nonscientist), will favor the hypothesis that tribalene is not an effective cancer therapy.

Likelihood among Background Data. We can also use this likelihood approach to determine if one piece of background information is more diagnostic than another by seeing how much their likelihood ratios differ from each other. If, for example, one ratio is slightly greater than 1 and the other ratio is considerably less than 1, the second ratio is not only more diagnostic, but it undercuts the first because its diagnosticity is not only greater but in a different direction.

This is the situation with our two pieces of background information about Siegel's psychotherapy hypothesis. One of the likelihood ratios consists of $\text{Pr}(\text{the source is a Cornell medical doctor, and so on} / \text{the psychotherapy is an effective cancer therapy})$ and $\text{Pr}(\text{the source is a Cornell medical doctor, and so on} / \text{the psychotherapy is not an effective cancer therapy})$. This ratio would end up being somewhat greater than 1. We can see that the ratio would be greater than one by noting how surprised we would be if the therapy is effective and we then found that its source was a Cornell graduate, and then noting how surprised we would be if the therapy were not effective and we found that its source was a Cornell graduate. We would be less surprised by the former circumstance than the latter because of the high standing of Cornell Medical School and the track record in medicine of its graduates by and large. When we are less surprised by the one circumstance than the other, we are indicating that we consider the former circumstance more probable than the latter.

The other likelihood ratio here consists of $\text{Pr}(\text{the source is a bad reasoner, and so on} / \text{the psychotherapy is an effective cancer therapy})$ and $\text{Pr}(\text{the source is a bad reasoner, and so on} / \text{the psychotherapy is not an effective cancer therapy})$. This ratio would be considerably less than 1 because its numerator would be many times smaller than its denominator—bad reasoners do not come

up with cancer cures, whereas bad reasoners do come up with ineffective therapies.

Methodologic Reasons for Prior Probability Ranking

We evaluate hypotheses in terms of how well they fit the data at hand as well as in terms of how well they satisfy methodologic criteria such as simplicity, generality, modesty, refutability, and precision (14). For example, other things being equal, if one hypothesis is simpler (or more general, more modest, more refutable, or more precise) than another hypothesis, that is a good reason for preferring the former to the latter hypothesis. It can also be a good reason for assigning a substantially higher prior probability to the former than to the latter.

Paranormal Therapies for Essential Hypertension. Consider, for example, two paranormal therapy hypotheses about treating uncomplicated essential hypertension: that "laying on of hands" can effectively reduce blood pressure in patients with essential hypertension, and that "healing at a distance" can effectively reduce blood pressure in patients with essential hypertension, where "healing at a distance" occurs when "the healer takes a patient in mind and healing occurs by thought projection." These hypotheses were tested in a clinical trial in The Netherlands and the results published in the *British Medical Journal* in 1988 (15).

If other things are equal, any normal competing hypertension hypothesis will be both simpler and more modest than these two, and so would have a higher prior probability than either of them. This is easy to see with the two paranormal hypotheses. Every hypothesis assumes that certain kinds of entities exist and that certain kinds of events occur. If one hypothesis assumes that there are only normal physical things and events in the world, while another assumes that there are both normal physical and paranormal non-physical things and events in the world, the first hypothesis is *prima facie* simpler and more modest—simpler because it assumes only one rather than two basic kinds of things or events, and more modest because it assumes more usual and familiar kinds of things and events than the second hypothesis.

Given these straightforward general points about estimating the prior probabilities of paranormal hypotheses, why did the Dutch investigators choose two paranormal hypotheses to test in a prospective, randomized (and largely double

blind) trial—indeed, a trial for a medical problem that must attract no end of normal therapeutic hypotheses? In the introduction to their article about the study, they say that they selected these hypotheses to test because paranormal healing has a long history, it has become more popular in The Netherlands and the United Kingdom in recent years, most patients (according to a dissertation by one of the Dutch investigators) report some improvement after paranormal therapy or treatment, and “no data are available on whether paranormal healing results in measurable improvement.” However, this sort of background information does not distinguish their paranormal hypotheses from scores of patently worthless occult hypotheses with a history—that is, hypotheses with prior probabilities that we can regard for all practical purposes as 0. It is perhaps worth noting that the Dutch Research Foundation for Paranormal Healing supported the clinical trial of paranormal therapy for hypertension.

Simplicity and Modesty as Criteria for Other Therapies. The NIH Office of Alternative Medicine has funded a study of intercessory prayer as a treatment for substance abuse, a study of the effects of therapeutic touch on immune responses to stress, and a study of Qigong therapy for intractable reflex sympathetic dystrophy. Prayer therapy hypotheses, therapeutic touch hypotheses, and Qigong hypotheses typically have the same problems as any paranormal hypothesis with respect to simplicity and modesty. They each assume there are unusual nonphysical things or events in addition to the usual physical things or events. Prayer hypotheses, almost by definition, involve spiritual (immaterial or nonphysical) things and events. Therapeutic touch is a current version of traditional “laying on of hands,” and therapeutic touch hypotheses usually involve an assortment of unusual paranormal energies, energy fields, and energy transfers. Qigong hypotheses involve the curious Qi energy that supposedly flows along meridians in the body as well as the opposing forces of Yin and Yang.

Explaining the Paranormal as Normal. Some people try to mitigate these methodologic problems by suggesting that if these hypotheses are eventually found to be true, we may also find that they involve nothing more than the usual assortment of physical things and events. For example, the Dutch investigators consider whether normal psychological factors—and not paranormal factors—might be involved in any changes in blood pressure in the group treated by “laying on of hands.” This suggestion does not change the status of the paranormal hypotheses. Rather, it

introduces a competing hypothesis (indeed, a normal competing hypothesis), and we need to estimate the prior probability of that hypothesis and then compare it to the other competing hypotheses.

Still others try to avoid these methodological problems altogether by indulging in high-technology rhetoric and conjecture. Larry Dossey is co-chairman of the NIH Office Panel on Mind/Body Interventions, which deals with prayer therapies. In his book on the topic (16), Dossey distinguishes traditional prayer hypotheses from his modern “nonlocal” prayer hypothesis that will be part of the new era in medicine, the era of “nonlocal or transpersonal medicine.” As he has done for more than a decade, Dr. Dossey presents an exaggerated and distorted account of quantum physics and then redescribes a therapy—this time intercessory prayer therapy—so that it sounds perfectly consistent with the latest ideas in physics (17). The prayer hypothesis becomes just another hypothesis about “nonlocal effects,” and so part of the grand unity of things that physics is beginning to tell us about, which in due course will become familiar to us.

Problems with Positive Cases

Although some proponents of alternative medicine may acknowledge that their hypotheses have problems with basic science, source considerations, and methodologic criteria, few proponents will acknowledge that their hypotheses have problems with positive cases. The success stories, the positive results with actual patients, the anecdotal evidence, the testimonials, the good outcomes in real people—these are supposed to be their strong suit. A positive case is a positive instance or application of a therapeutic hypothesis. If the hypothesis is that a therapy is an effective therapy for localized non-small-cell lung cancer, where “effective” means (for the sake of illustration) a complete remission or response, a positive case is a patient who receives the therapy and in whom all signs and symptoms of the lung cancer disappear for at least four weeks. If anything should seemingly be part of the relevant background information that bears on the truth of a therapeutic hypothesis, it is information about positive cases. Indeed, a number of positive cases for an alternative-therapy hypothesis might seem like a good reason for raising the prior probability of the hypothesis above what it would be without these positive cases.

Gerson Therapy. Consider Gerson therapy for cancer and other “chronic, degenerative diseases” such as multiple sclerosis, rheumatoid ar-

thritis, diabetes, and systemic lupus erythematosus. The therapy hypothesis is that a special dietary regimen and "detoxification" procedures amount to an effective treatment for these diseases, where the diet is (among other things) low in sodium and high in potassium, and the "detoxification" procedures emphasize coffee enemas. In 1958 Gerson published a book that explains the rationale behind this therapy as well as the details of his dietary regimen (18). This book also presents 50 positive cases. The Gerson Institute has promotional literature, books, and videotapes that present even more positive cases. Given these positive cases, it might seem that we should raise the prior probability of the Gerson hypothesis above what it would be without these positive cases. Benjamin Brown, writing in the *Journal of the American Medical Association*, wants to raise the prior probability a great deal because of positive cases like these. Brown claims that "much medical advancement has come through empirical identification of success, with discovery of the correct rationale sometime later" (19). He maintains that "the Gerson therapy has been in circulation long enough, roused enough lay interest, and shown enough startling anecdotal success to warrant proper scientific studies." When Brown refers to "startling anecdotal success," he is referring to positive cases.

The first thing we should recognize about positive cases is that virtually (if not literally) every alternative-therapy hypothesis has positive cases, yet not every alternative-therapy hypothesis is true. Even proponents of alternative therapies agree that some alternative therapies are totally ineffective (and thus that the corresponding therapy hypotheses are false). For example, the medical writer Patrick McGrady, who runs the CanHelp resource service for cancer patients, claims that most alternative cancer therapies are "almost totally useless" (20). It is almost axiomatic that if a therapy has been in use for a period of time, some patients will have received the therapy and will also have experienced a positive outcome of their medical problem. The therapy may have caused the positive outcome, or it may not have. A positive case does not tell us about cause and does not distinguish the true from the false therapy hypotheses; positive cases alone do not change the prior probability of a hypothesis.

Positive Cases and the Laetrile Hypothesis. In the late 1970s, the National Cancer Institute (NCI) attempted to bring data about positive cases to bear on the laetrile hypothesis by soliciting positive cases—patients supposedly showing a good antitumor response—from health profes-

sionals. The NCI wanted "to determine whether enough evidence of possible antitumor activity can be documented to justify undertaking a prospective trial" (21). Among other things, the NCI asked for fully documented cases in which the patient had measurable disease, had received laetrile for at least a month, and had not received any conventional cancer therapy during that month or the month prior to starting therapy with laetrile. The NCI judged the cases in terms of the standard criteria for a complete, partial, or mixed response (for example, by comparing radiographs over time). The judging was done by a panel of twelve experts in oncology that reviewed a summary of each case and arrived at a consensus opinion on it by voting. The panel actually received a mix of case summaries—those summarizing the cases treated with laetrile and others summarizing cases treated with NCI investigational drugs—and was kept ignorant of which cases were treated with which agent. This step was taken, of course, in order to rule out the effects of any bias when conventional oncologists looked at unconventional therapies. The panel reviewed 67 laetrile cases and judged 2 of them to be complete responses and 4 of them to be partial responses (22).

How did this positive case information bear on the laetrile hypothesis? Did it, for example, change and perhaps raise its prior probability? Even the NCI investigators did not seem to know. In their primary article on this inquiry (23), they waffled back and forth over what this information means. It is possible, they noted, that laetrile actually produced the 6 positive responses, but "the design of this study in no way allows us to draw this conclusion." They also noted that they could not compute a response rate here because they did not know what the denominator was (it could have been anywhere from 67 to more than 67,000). The NCI had only solicited positive cases or those cases believed to be positive, and a meaningful denominator would include both positive and negative cases or those believed to be negative as well as positive. The investigators discussed other possible explanations for these responses (spontaneous regression of a tumor, the natural history of some tumors, falsified or omitted data) but they did not choose one explanation as both possible and probable. In the end, they simply concluded their primary report by saying that "it illustrates the difficulty of drawing inferences about therapeutic efficacy in the absence of properly designed randomized trials" (23).

In the end, therefore, it seems they did not know what to do with this positive case informa-

tion. They did not, it seems, have a good idea of how to draw conclusions from it, no matter how many partial or complete responses the panel claimed to find in the collection of laetrile cases.

Positive Cases and Cancer Therapy. The same problem arises with the latest recommendation from the Office of Technology Assessment (OTA) about positive cases and cancer therapies. In the late 1980s, the OTA considered bringing information about positive cases to bear one way or another on alternative cancer therapy hypotheses. In the last chapter of their report on alternative cancer therapies (7), the project's staff endorsed the NCI solicitation of positive cases in connection with laetrile. They called this approach a best-case review for tumor shrinkage. They maintained that the original NCI plan needed only a few changes (including greater participation by alternative practitioners in the process) to be used "more prominently in determining" which alternative cancer therapies "might deserve further investigation." Each positive case must have a fully documented diagnosis, a full history of all previous therapy, a statement about the time period between the last (presumably conventional) treatment and the current, unconventional treatment under review, a set of radiographs before the unconventional treatment began and after it had run its course, and a statement affirming that the patient was not given any other treatment along with the unconventional treatment under review. The OTA wanted a panel of experts to review these best cases and to determine how many were complete or partial responses.

What will one result mean as opposed to some other? For example, what should we conclude if there is at least one partial or complete response in the collection of best cases? The OTA does not say a thing about how they, or anyone else, should draw a conclusion from a collection of cases that have been judged for tumor shrinkage by a panel of experts. Nonetheless, the OTA project staff maintained that "an adequate and convincing review could be based on as few as 10 or 20 successful cases."

This is not just an idle academic problem. The OTA really wants alternative practitioners to assemble collections of best cases. In their report, they claim that the Gerson Institute is in the process of doing just that. Moreover, the NIH Office of Alternative Medicine has adopted the best-case approach. In the July 1994 issue of *AM*, the monthly newsletter of the Office, is an article about the Office's cancer workshop (24). The workshop had a session on the best-case ap-

proach, and one alternative practitioner presented 3 of his 25 best cases. The article also reports that the National Cancer Institute's Division of Cancer Treatment has used the best-case approach since 1991. The division supposedly developed this approach "as part of its search for possible new cancer therapies" and it allows them "to explore possible therapies from a very wide range of both orthodox and alternative research." The article also maintains that "if a therapy presented in this manner seems to merit further investigation, NCI may fund Phase II and, if indicated, Phase III clinical trials." The newsletter also carries a report by the alternative practitioner on his 3 best cases. The practitioner ends his report by saying that NCI wants him to "carry out a closely monitored 1-year pilot study of 10 patients with pancreatic cancer." Apparently his alternative cancer therapy "merits further investigation."

Best-Case Review: A Phase II Trial? This is also not a minor problem. Suppose that an alternative practitioner sends in a collection of 20 successful cases, an expert NCI panel judges these cases for tumor shrinkage, and the panel determines that all 20 cases show positive responses in measurable disease. This is a very good best-case review. Since the OTA believes that these best-case reviews can be convincing, these results should demonstrate that the therapy in question merits further investigation. If these are convincing results, then $\text{Pr}(\text{they would see 20 such cases/ the therapy hypothesis is not true})$ should be low.

However, there are some straightforward reasons for thinking that this probability will be high if things go as the OTA expects here. The OTA believes that the best-case approach will be an efficient way to produce relevant information for therapies that have been "used by hundreds or thousands of patients." Suppose that an alternative practitioner starts by treating 14 patients with solid tumors, and none of them have a positive response in measurable disease. This does not deter the practitioner, and he continues treating patients. Indeed, suppose he treats another 45 patients, and one of them has a positive response in measurable disease. The practitioner now has his first case for his collection of best cases, and so he sets it aside. Suppose that things proceed in this fashion with the next 59 patients. The practitioner then has his second best-case. If things proceed in this fashion eighteen more times, the practitioner has his 20 best cases, each showing what counts as a positive response. He will have seen a total of 1,180 patients in 20 different groups of 59 patients per group.

We can view each of these groups as a Gehan two-stage phase II clinical trial of a new chemotherapy drug, where the same drug is studied in each trial. An uncontrolled phase II trial is supposed to determine whether a drug has any anti-tumor activity, and its results are used to make decisions about whether a drug merits further investigation. The Gehan phase II design (25) has been the most commonly used design in phase II chemotherapy trials. If we want to use this design to make a decision about a drug, we need to specify an interest level and a rejection error level. Let us suppose that we are only interested in pursuing a drug if it is effective in at least 20% of patients and that we accept a 5% rejection error—that is, in this context, we take a 5% chance of failing to investigate a drug further when the drug actually merits further investigation. These are standard levels for a phase II trial of a chemotherapy drug for relatively unresponsive solid tumors.

The first stage of a Gehan trial for our supposed drug consists of 14 patients, and we do not proceed to the second stage unless we see at least one positive response. If the drug is effective in at least 20% of patients, then (on the probability model of the Gehan design) there is a 95% chance of seeing at least 1 positive response in 14 consecutive patients. If we see at least 1 positive response in the first 14 consecutive patients, we can proceed to the second stage of the trial. The second stage consists of 45 more patients, and this stage allows us to estimate the true response rate of the drug with a standard error of approximately 5%. If a drug does not reach stage two, it is deemed worthless and discarded. Since our practitioner does not see even 1 positive response with his alternative drug, he should deem it worthless and discard it. However, he continues (in effect) to stage two of a Gehan two-stage trial and sees a positive response that he sets aside as his first of 20 best cases.

The supposed drug receives (in effect) twenty phase II two-stage trials and yet it does not warrant passing into stage two in any of these twenty trials. It should be discarded twenty times over. It only continues into stage two because an advocate is in charge of things instead of an investigator. Of course when our practitioner sets aside each of his best cases, the response rate is less than 2% with a 95% confidence interval that includes 0% and has an upper limit of less than 3.4%. Each of his best cases is nothing more than a spurious response because the supposed drug plainly does not merit further investigation. The chances of this scenario happening depend (for the most

part) on how many cases a practitioner treats and how frequently spurious responses occur.

We can obtain one estimate of spurious responses from a review of 26 discontinued anticancer agents (26). The authors add together the results from various studies of these agents and report that 15 of the 26 agents have at least 2 responses per 14 patients in phase I and phase II trials. That is, they found at least a 7% response rate per 14 patients for 56% of the agents. They found this rate in anywhere from a total of 15 patients to a total of 607. If we add together the results of our alternative practitioner, the response rate is a mere 1.7% per 14 patients for a total of 1,180 patients. Presumably more than 56% of the discontinued agents would have a 1.7% response rate per 14 patients treated. In addition, it seems reasonable to suppose that the chances of seeing spurious responses in patients increase as we treat more patients with the agent. If an alternative practitioner treats 1,180 patients, we might estimate that he stands a 65%–70% chance of seeing 20 spurious responses even though he is treating patients with an ineffective agent. If he sees these responses and does not deem them to be spurious, he has the makings of an OTA best-case review.

Summary and Conclusions

The most important thing we have to decide about alternative therapies is whether to test them in a clinical trial format. In order to decide this, we need to compare the prior probabilities of alternative therapy hypotheses with the prior probabilities of conventional therapy hypotheses that end up in clinical trials. If the prior probabilities of the alternative therapy hypotheses are lower than the prior probabilities for their competing conventional hypotheses, we do not have a good reason to test them.

There are basic science reasons, source reasons, and methodologic reasons for assigning low prior probabilities to typical alternative therapy hypotheses—indeed, hypotheses that the NIH Office of Alternative Medicine supports. Basic science reasons are of two types: whether the hypothesis agrees with a piece of basic science that does not have a good deal of support, and whether the hypothesis is logically incompatible with a well-supported piece of basic science. The source reasons are about the educational and other characteristics of the people who discover, pursue, and promote a therapy hypothesis. The methodologic reasons are about how well a therapy hypothesis satisfies methodologic criteria such as simplicity

and modesty. Other things being equal, a hypothesis that is simpler and more modest than another is more plausible as well.

Problems arise also about using positive cases in assigning a prior probability to an alternative-therapy hypothesis because virtually every alternative therapy has positive cases, but not every hypothesis is true. The NCI and OTA "best-case" review approach does not solve this problem because it does not include a rule for distinguishing (in a reliable way) between positive cases that show something about a therapy hypothesis being true and positive cases that show nothing of the kind.

This paper (as long as it is) is no more than an introductory discussion of some basic points involved in making sensible estimates of the prior probabilities of hypotheses. Nonetheless, the NIH Office of Alternative Medicine has a congressional mandate to test alternative-therapy hypotheses in a clinical trial format. The Congress allocated \$3.342 million to the Office for 1994 and \$5.4 million to the Office for 1995. If the points in this paper are even halfway correct, the Congress should find something better to do with its money.

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Cases and Doubts

AVI BARBASCH, M.D., AND LINA SHIHABUDDIN, M.D.

TWO CASES raising a variety of questions about alternative medicine are presented below, and each is followed by a discussion of the case by the case presenters and their colleagues.

Case 1: Chemotherapy vs a Macrobiotic Diet

Avi Barbasch, M.D.

A 57-year-old man had a history of smoking, approximately two packs of cigarettes per day over 35 years, and a history of heavy ethanol intake over 20 years. For the three months preceding his visit to my office, he had experienced progressive dysphagia, first to solids, then to liquids, and he had essentially stopped eating and had lost about 30 pounds by the time he came to my office.

On evaluation he was found to have a lesion in the upper third of the esophagus; biopsy results were positive for squamous cell carcinoma of the esophagus. He was also found to have multiple enlarged lymph nodes, presumed to be metastases, in the mediastinum and the upper abdomen.

The nature of the illness was fully explained to both him and his wife, and the various conventional therapeutic modalities—specifically chemotherapy, radiotherapy, and surgery—were described. The patient's response was that I should

do anything which I thought appropriate to make him better. A four-day chemotherapy infusion regimen was begun.

He returned to my office for reevaluation two weeks following discharge from the hospital. At that time he described the absence of any pain as well as his ability to eat absolutely normally; he had also put on 5 pounds since his last visit. He went on to inform me that he had decided to stop his chemotherapy at this time. He told me that though he tolerated the chemotherapy well and recognized its benefit, he wanted to try a macrobiotic diet regimen instead of the chemotherapy.

Two months later he came to my office again with dysphagia and marked weight loss. He was hospitalized for terminal care.

Questions and Answers

Question: Did the patient explain how he came to know about the macrobiotic diet?

Barbasch: He knew no one who had a personal experience; he had read about it. I have my own theories about why he chose it, but they have nothing to do with how he knew about the diet.

Question: Did you try to persuade him?

Barbasch: Very much so. This was a lengthy process. I worked on him, then I worked on his wife, then I worked on him again, then on both of them. None of it worked.

Question: For those of us who are not oncologists, could you give us a brief summary of his anticipated prognosis with and without chemotherapy?

Barbasch: There is a varied response rate to chemotherapy in cases where the disease is as advanced as it was in this man. The literature shows a range in response rate of between 15% and 80%, the majority of results falling somewhere around 30% to 40%. The median survival rate ranges from 3 to 9 months; the bulk is somewhere around 4 to 6 months, that is with treatment, with chemotherapy.

Adapted from the authors' presentations at the medical ethics conference "Science, Alternative Care, and Third Party Payers," March 18, 1994, Mount Sinai Medical Center. From the Department of Medicine (AB) and the Department of Psychiatry (LS), Mount Sinai Medical Center, New York, NY. Address reprint requests to Avi Barbasch, M.D., Asst Clinical Prof. of Medicine, Dept. of Medicine, 1050 Park Avenue, Mount Sinai Medical Center, New York, NY 10028; and to Lina Shihabuddin, M.D., Psychiatry Fellow, Dept. of Psychiatry, Box 1230, Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029.

Question: So additional survival is several months?

Barbasch: That is correct, at best.

Question: What is the quality of life in the last 3 months of survival?

Barbasch: If treatment works—and this patient is a good example of that—the patient can eat and function better. The patient was in fact able to do that for a short time.

Question: What reasons did the patient give you for wanting to try the macrobiotic diet? Did you explain to the patient his life expectancy with treatment? Third, how much did you know about macrobiotic diets when he brought it up?

Barbasch: When he first brought it up, I did not know very much about it, a little bit. After he brought it up, I read a lot about it. I learned all about the East West Institute, the specifics and theories behind a macrobiotic diet, and about the foods, so that I could at least, depending on how much knowledge he had, have a reasonable discussion with him. Also, I wanted to see whether there was some validity to it. I had had one other experience prior to this case. Someone went to the East West Institute in Boston to be trained and brought a cook back from there to their home. What I saw was that this person lost a lot of weight because he was used to a Western diet and could not really tolerate the change—and it is a significant change in eating habits. I explained this to this patient, I explained about the outcomes, I explained his prognosis.

As for the reason why he wanted to do it, he would not elaborate, other than to say it was a personal preference. He had the belief that the macrobiotic diet was better, even though he recognized the improvement that he had already had with the chemotherapy.

Question: It is clear that you are at a therapeutic end-point with this individual, and that has to be a real conundrum for you and other practitioners. In my view, this is a further reason supporting the idea that conventional oncologists and people like yourself ought to be engaged in the evaluation of how patients are benefited or not benefited by these therapies. I think where the alternative medical community really falls down is where they purport cures, clinical cures. When anyone says they have a cure for all diseases, I laugh because I cannot accept that level of intellectual dishonesty.

However, I think it is not unreasonable to iterate backwards off the term “cure” and look at how patients are benefited by this. Someone raised the question of quality of life; the individual's quality of life may have been enhanced,

even though his survival may not have been enhanced even one day. I think the issue has to be brought back not only to supporting the patient's belief system, but also to noting how supporting their belief system enhances their quality of life.

Barbasch: I have to tell you that I personally was distressed, not because he chose to seek an alternative medical care but because there had been a response to the treatment he received. Had he not benefited at all, I would not have attempted to persuade him. But here I saw someone who derived some benefit, meaning he was one of the people that responded to chemotherapy, and so I thought that to discontinue was poor judgment. One could, if the patient had asked, combine modalities—that could have been done. Or if he had brought up the idea of trying a macrobiotic diet when conventional treatment had failed, I think that also might have been a reasonable plan.

Case 2:

Gastric Lavage vs Neuroleptics

Lina Shihabuddin, M.D.

The patient is a 45-year-old plumber successful in his work who has a wife and three sons. He is a religious Muslim who believes in angels and demons. He has episodes of feeling demons in his stomach and getting a message from the Prophet's wife to have a gastric lavage. These episodes started when he was 23 years old and happen three to four times a year. At such times he comes to the emergency room with his family and they all insist on his being given the lavage. He gets the lavage and goes home free of “demons” until the next episode a few months later.

The patient grew up in the neighborhood, was a single child, and dropped out of ninth grade because school “was not for him.” His neighbors describe him as a “funny strange guy but a very good plumber.” At times he has been seen talking to himself while on the job, dressing eccentrically, and posturing in a weird manner in the street, but he never bothers anybody and is always pleasant. According to him and his family, his life is “peaceful and uneventful” except for the episodes, which—despite his belief in angels and demons—are outside the realm of his religion.

On several occasions he was evaluated by a psychiatrist and found to meet the criteria for chronic paranoid schizophrenia (1). He and his family refused any kind of psychiatric intervention and insisted that his experiences were real and normal.

The Dilemmas: Medical, Ethical, and Financial. This case poses a medical dilemma for the psychiatrist. Should she hospitalize this patient and treat him with neuroleptics against his will, knowing there is only a 30% chance that he will respond? Or should she leave him alone, allowing him to continue to use the power of suggestion (2) with gastric lavage to temporarily relieve his symptoms? He is not a danger to himself or to others, except in the sense that his three sons (ages 14–18) are adopting his beliefs in a “shared delusion” phenomenon. Otherwise there is no evidence of abuse or neglect of the children.

From an ethical perspective the problem is, should the psychiatrist respect this person’s autonomy and his choice of refusing treatment with neuroleptic agents, or should she force treatment on him even though doing so would tear his family apart and deprive them of their only source of income? The answer seems to depend on whether the question is viewed from a physician’s perspective or from the perspective of civil rights—protecting the right of an individual to accept or reject treatment.

The question of costs also arises: paying \$200 three or four times a year for gastric lavage, or paying \$600 per day for a lengthy hospitalization and expensive drug regimen. Given what we know about the course of schizophrenia, hospitalization and drug treatment would be a process repeated over many years.

Questions and Answers

Question: How would you feel if you did the lavage and he aspirated and died?

Shihabuddin: If you give him neuroleptics he develops neuroleptic malignant syndrome or tardive dyskinesia. Each entails risks and benefits. Actually, the chance that this patient is going to aspirate during a properly done gastric lavage, is much less than the risk of him developing tardive dyskinesia. He is going to have lots of problems from the neuroleptics; the treatment is not easy. We do not have a cure for schizophrenia that is free from risk.

Question: Would you put him to sleep and just tell him he had had a gastric lavage?

Question: It is a placebo, is it not?

Shihabuddin: The gastric lavage is working, we believe, through the power of suggestion—that is what is happening with this man. In psychiatry we use this a lot, and I guess everybody does. We use it with hypnosis and in psychotherapy we use lots of suggestion. He will not go to sleep, he will not take any medications. You would have to

forcefully do it, and then it would not work, because the power of suggestion operates through the gastric lavage.

Question: I am not sure I see what the ethical problem is here. Why is it any more ethically dubious to give him this treatment that he wants and presumably can pay for than it would be for somebody who sells toupees to sell me a toupee because I think it will make me extraordinarily handsome and irresistible, even though it will not? It is his choice.

Shihabuddin: I do agree with you, if we want to give him the choice; but how many internists will give this man a lavage without calling a psychiatrist, and how many psychiatrists would write, “It is his choice. . . .”?

Question: Is that not a problem with internists and practices?

Shihabuddin: Of society, I guess. In my country, Lebanon, where this took place, there was no problem. This man would come in, get his gastric lavage, and go home. We cannot afford institutionalizing these people, we cannot afford to treat them, so we just do whatever works.

Question: This is a classic case of cross-cultural medicine and interpretation of value systems across two different cultures. In fact this case could be repeated on a Navaho reservation in the Southwest. In Arizona, similar issues would arise. In fact, I suspect that some physicians in the Indian health service would feel relatively comfortable with such decisions, understanding the belief systems operating in the community and knowing that patients are going to ask for certain things and have certain expectations. It is a little difficult for us to do it because we are in another cultural environment, but I think one has to take into consideration some of the cultural norms and also cultural taboos.

You are absolutely right, this is a dilemma. I do not think it is that far from alternative medicine, because I think it underlies many of the conflicts that we deal with in terms of alternative medicine.

Question: Let me add a point to that. I do not think we even need to think about it on a cross-cultural basis. There are millions of Americans who use colonic irrigation. Basically, there is a belief among a significant portion of the public in the doctrine, long ago disproved by medical science, of autointoxication. There is the belief that there are poisons throughout the body—they do not need to be demons, they are poisons—and they have to be flushed out. Individuals believe they regularly have to take this type of therapy, in order to maintain their health. It is not so un-

usual a belief and I would not want to restrict it, to say that this could happen only in Lebanon—and not to consider that this is a practice regularly engaged in by millions of Americans.

Shihabuddin: It is a dilemma when you have a medical degree and you are sitting in the emergency room and someone comes in and says, "I want enemas because I have poison in my colon."

Question: Anyone can take an enema by themselves. We are introducing another serious ethical dilemma because you are suggesting that the physician participate in the delusion. In doing so, the physician knowingly supports the delusion and becomes an active participant. I think that physicians have ethical responsibilities, and one of them is not to do whatever the patient demands on the basis of a delusion, whether on a Navaho reservation or in Saudi Arabia. I think for anyone practicing Western medicine, according to Western ethical precepts, there are certain things we do not give patients, whether it is crack or heroin or washing out their stomachs.

Question: What about cosmetic plastic surgery? Somebody who looks perfectly fine to you—maybe has a little bump—undergoes the risk of dying from anesthesia for a cosmetic surgery.

Shihabuddin: Most third party payers will not pay for that.

Question: That is right, but physicians do it.

Question: But what if this man was taught to do lavage himself, which leaves out the issue of the relationship of the patient to someone?

Shihabuddin: I believe that unless a physician administered it, it would not work.

Question: We are assuming that this is not going to get any worse and that it is not going to affect his family. You are assuming that taking him away from the family, if in fact that is the only other option, is actually worse.

Shihabuddin: He is a chronic schizophrenic and has been since he was 23 years old, as far as we can tell—that is 20 years. He has paranoid schizophrenia, which has a better prognosis than anything else. He can work, he does not have a formal thought disorder, he has only an isolated delusion, which makes for a better prognosis. Even so, only 30% of such people would respond to neuroleptics. Because he is refusing psychiatric treatment, the only way a physician could do it is by putting him in the hospital, putting him in restraints, giving him intramuscular medication, which means tardive dyskinesia, and so on. There is no real alternative, yet, of treating schizophrenia.

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Multiculturalism, Alternative Health Care, and Responsibility for Belief

WILLIAM FISK

WHEN THE PRELIMINARY LIST of speakers at the conference on which this section of *The Mount Sinai Journal* is based appeared, it seemed unfortunate that it contained no representatives or advocates of what we are calling "alternative health care." They, after all, are the objects of all this talk, and it seems—one way or another—to be impolite to exclude them altogether from a discussion of what they do.

Reasonable Exclusions. There are, to be sure, reasons for excluding categories of persons from speaking at a conference. Those who deny that there ever was any such event as the Holocaust (as against those who have reservations about the grotesque political uses made of that all-too-real event) are not deserving of any but dismissive attention. Even a conference on Holocaust denial could, with good conscience, refrain from inviting any Holocaust deniers. This is so because they defy the weight of irrefutable evidence, and at that can best be understood as doing so for morally questionable reasons.

Again, one might well not bother to invite any sufferers from cancer to a conference on some new chemotherapeutic treatment modality. Here, the exclusion would emphatically not be based on the irresponsibility of cancer sufferers when it comes to forming beliefs, but rather on the irrelevance of what they might have to say. The pharmacologic and physiologic details of the workings of some chemotherapeutic agent on the human

body are just not something that the cancer sufferer, unless she also happens to be an oncologist, can be expected to know much about.

Yet again, one might exclude a class of persons from a conference on the grounds that they belong, so to speak, to another tribe—that they are not part of the community to which the conference is legitimately restricted. Males, for example, might legitimately be excluded from speaking at a conference on women's experience, for all that they have occasionally, for better or worse, impinged on the experience of females and so might have something relevant to say about it.

Clearly the exclusion of alternative health care practitioners from this conference falls either into the first or the third of these categories—unless it falls into some mix of the two. Their points of view are not irrelevant, so they are either objectionably irresponsible in the way they come to form their beliefs, or they belong to another tribe, another community, which it is quite allright to exclude.

There may well be plausible excuses for this exclusion. It is imaginable that, had an alternative health care practitioner been invited to speak, that practitioner might subsequently include the phrase "as presented at Mount Sinai School of Medicine" in a résumé or advertising—an inclusion that could doubtless upset some local bigshot, not without cause. Engaging persons in conversation, particularly in a formal setting, suggests at least a minimal endorsement of their views, and such "endorsements" can be exploited. What is more, the presence of holistic health care gurus and their acolytes at such a conference might well lead to acrimony and mutual incomprehension. A conference in which the phrase "you don't know what you are talking about" is heard repeatedly is arguably not something to aim at.

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Multiculturalism and Inclusion

Since no members of the alternative health care community had been invited to this conference, I thought it might be useful to examine an argument in favor of an inclusive or generous attitude toward alternative health care practices. Since the conference is apparently otherwise neglectful of the array of non-Western traditions and communities that form a significant part of the alternative health care movement, it seemed worthwhile to look at the role of multiculturalism in this issue. Some of the considerations that may bear on the exclusion of alternative health care advocates from this conference—the bestowal of legitimacy, inclusion in a community, and responsibility for one's beliefs—are central to the argument I wish to examine.

One might defend an inclusive stance toward alternative health care on the basis of something called "multiculturalism," a word more likely to be heard at the NEH than at the NIH. "Multiculturalism" is altogether a trendy and annoyingly elastic bit of jargon, but it has its uses. I take it to refer to a belief that our institutions should acknowledge, respect, and express the diversity of cultures that make up our society. By a "culture" I mean a comprehensive system of beliefs and values rooted in, and in turn rooting, a shared way of life. Those who would be multicultural are obliged to be attentive and responsive to the varied cultural perspectives of others and, in their own lives, to seek—where this is relevant—to integrate their distinctive cultural heritages rather than submerging that heritage in the cosmopolitan waters of the dominant culture.

Respect for Persons. Multiculturalism, on this account, would seem to be just a special application of the venerable and quite fundamental ethical attitude of respect for persons. Traditionally that attitude has been thought to have its basis in our rational or moral natures. The multiculturalist calls attention to the importance to personhood of participation in a particular historically developed and developing, socially shared way of making sense of things. Morality may apply, the multiculturalist points out, to (at least) all rational beings, but—on this planet at least—no person is just simply a rational being. Rather, all human persons are beings whose rationality, humanity, capacities for participation in a moral community take shape, are articulated by, and find expression in highly specific and quite diverse ways of life.

The extreme forms of the multiculturalist view take cultural identity to be in virtually all respects the paramount fact about persons. The

reasonable view merely says that some transcultural features of human beings, for example rationality, are only met with in culturally conditioned forms and that this fact demands more serious attention than it has generally received.

It is not hard to see how multiculturalism affects, say, the ways we are to think about history. The history that most interests most of us is the history of how "we" came to be as "we" are. As a runner-up, "we" are interested in the history of periods in the lives of peoples who are in one way or another exemplary for "us." Multiculturalism asks us, critically, to make explicit just who "we" are supposed to be and, more positively, it encourages us to enlarge our sense of "we" or, if you like, fully to recognize the multitude of "we's" the ensemble of whose histories form a yet larger story in which all of us are participants.

What do these vague and somewhat utopian suggestions have to do with health care? Recall that the characterizations of the term "culture" offered above include such phrases as "way of making sense of things" and "shared way of life." Being mortal and subject to bodily affliction and infirmity, humans cannot count as a way of life anything that does not include beliefs and practices concerning health and illness. If a culture is—*inter alia* at least—a way of making sense of things, and if, as is undoubtedly the case, some of the things of human life that most urgently need to be made sense of are the rude facts that we get sick and die, it is only to be expected that cultures, systems of beliefs and values and the practices that embody them, should provide means of dealing with illness, health, and mortality.

If the multiculturalists, who take themselves to be the real respecters of concrete persons—as against the philosophically moralizing respecter of mere abstract personhood—are right, then ought we not to allow room in our public institutional structures for Navaho sings, voodoo ceremonies and the like?

The Role of Beliefs and Facts

Multiculturalism and a Functional View of Beliefs. The answer to this question, the response to the argument it expresses, depends on what one means by "making room." Physicians who know so little of the belief and value systems of their patients that they fail adequately to communicate with them have clearly failed to make room, in a way that is morally objectionable. The concern here, however, is with who pays the bill, and for what. The multiculturalist argument for

openness to alternative health care practices rests essentially on a view of beliefs that is sociological and psychological, a functional view of beliefs as means by which sense is made of things, by which human experience is rendered intelligible and manageable, as instruments for coping.

Rational Justifications of Belief. Beliefs, without a doubt, serve these functions. They also stand in need of justification, however. To justify a belief is to give reasons to take it to be true. Good reasons to believe something, in this justificatory sense, do not depend on the instrumental value of believing that thing. Which is not to say that good reasons aren't useful.

Imagine asking a stranger how to get to the American Museum of Natural History and being given directions that will land you in Nowhere's proverbial middle. If, after following the proffered directions and finding that they failed to lead where they ought, you chanced upon the one who had so directed you, you might ask why those directions had been offered. If the giver of cockamamie directions offered, as the reason for giving them, the response "I'm from Nepal," you would probably not find your discontent much allayed. Whether you are Nepalese or from the Bronx, the museum is in a certain place, and the route one ought to take to get there from some given other place is, in the main, quite independent of facts about the culture whose heir you happen to be.

The possibly simple-minded but probably correct claim that I wish to make is that what goes for the location of the Museum also goes for the maintenance of health. Of course, the location of a thing is only minimally vague, whereas whether an organism is healthy or not, much less how healthy it is, can be extremely vague and vexing—particularly if the organism is as complex as you or I. To say that health is a vague concept is only to say that there are instances in which it is hard to tell whether the concept applies. We are not, however, obliged to think, as we might be in the case of physical beauty, that health is culturally relative. In a vast range of cases, the answer to whether someone is healthy is a fact, whatever she or her culture might think. And there are, in a vast range of cases, facts of the matter about what will make her well, whatever she or those of her culture are inclined to think or do. That a belief about illness and how to cure it is expressive of one's culture is not the least bit relevant to its truth or falsity and so, in one important sense, lends it no justificatory force.

Having certain beliefs can have all sorts of consequences. The sociological, psychological, and functional view of beliefs concerns itself with

the consequences of holding beliefs. It may be good for one to believe something, in the sense that one's well-being is in one way or another enhanced by virtue of believing that thing. "I am pretty," "This is the greatest nation on earth," "My cancer is due to my pessimistic attitude and will be cured if I take a more positive approach to life" are all beliefs that can have desirable pay-offs. It is too much to demand morally of frail, vulnerable human beings that we not fall prey to believing things on the basis of the payoffs that such believing offers.

Rationality in Public Institutions. But it is reasonable and fair to ask of our public institutions, which in some fashion express our considered agreements on how we ought to pursue commonly arrived at purposes, that they should be answerable to public criticism, and subject to rational criticism.

I take it that many alternative health care practices rooted in various non-Western cultures and traditions have not yet withstood the sorts of rigorous attention to the justification of the beliefs which support them to which standard medical practices are (for all the embarrassing faddishness and hastiness with which therapies are sometimes embraced by the medical community) regularly subjected.

I also take it that health insurance, as we have it here and now, is sufficiently bound up with our government that to offer insurance for a given therapeutic activity is expressive of a public agreement on the acceptability, that is, some minimal sort of approval, of that therapy. Thus, if we offer insurance for a rationally ill-grounded practice, we are giving public acceptance to irrationality. And that, I think, we ought not to do, if our society is to be based on mutual respect. You and I respect one another when, if we are engaged in a common project, we are ready to offer one another reasons for what we think should be done to further our common aim, and are ready to accept criticism of those reasons. Health care is not essentially an expressive business, it is not a matter of saying who we are and how things seem to us. *Vis à vis* our expressive activities, it is not at all improper that we should publicly support a cacophonous multitude of voices and viewpoints.

But health care is centrally an instrumental matter. For all our diversity, sickness and health are among the things that, with plenty of vagueness around the edges, transcend culture. Our common aim, in health care, is the preservation of health. That common aim implies a common standard for the judgment of the means employed to achieve it. In a large core of cases, there is no

dispute about what health is. That health matters is also not in dispute.

Conclusions

To avoid misunderstanding, I emphasize what I have not been meaning to suggest:

- Different cultural groups in this society fare differently in matters of health and illness, to a degree that is, I think, scandalous. Qualms about a multiculturalist argument for openness to different health care practices do not in the least imply qualms about the need to ensure that the differences in healthfulness between our different peoples be lessened drastically.
- Nor is this paper intended to suggest, absurdly,

that there is no merit at all to any non-Western medical tradition.

- Nor have I in the least meant to suggest that a hospital would be acting incorrectly if it allowed literal room for the traditional healing practices of members of the local community.

That we should bankroll therapeutic practices on the basis that some folk or folks are profoundly attached to them is a dumb idea. However, to return to the qualm with which this paper began, the idea that we should not even talk to others, but only talk about them, is quite equally dumb. Which therapies are publicly supported should be decided on the basis of rational, critical discussion. To deny others the chance to take part in the discussion is to subvert the legitimacy of that discussion.

Alternative Medicine and Health Insurance

ROBERT A. PADGUG, PH.D.

"ALTERNATIVE MEDICINE" is scarcely a unitary and internally consistent category. It includes a wide variety of treatment modalities that do not easily coexist, are based on different theoretical and practical approaches and attitudes to the body and its ills, are derived from divergent cultures, and have widely varying rates of utilization and success. What approach can reconcile in a single intelligible grouping such disparate phenomena as Chinese acupuncture, chiropractic, holistic medicine, the occult, organic and natural food diets, homeopathy, biofeedback, faith healing and prayer, crystals, folk medicine, and the many types of herbalism—among others?

Some observers do see common general features beneath the confused mass: for example, that all alternative medicines stress personal responsibility for health and a strong role for prevention (1, 2); or, in contrast, that all are examples of medical "quackery" (3). None of these attempts at positive definition works well or assists very much in attempts to understand the nature of alternative medicine. It is more useful to assume that the category is "catchall" and to define its contents negatively, that is, by contrasting it with what it is not. This is the approach taken by David Eisenberg and his colleagues in an important 1993 survey of the utilization of alternative therapies by Americans, in which what are called "unconventional therapies," are defined simply as "medical interven-

tions not taught widely in U.S. medical schools or generally available at U.S. hospitals" (4).

This definition, vague as it necessarily must be, points in a useful direction: alternative medicine consists of approaches and therapies that are opposed to or, for one reason or another, remain outside what we may term, for convenience and without further definition, modern "scientific medicine" as it has developed and flourished during the 19th and 20th centuries.

"Scientific Medicine"

These major components of scientific medicine, or what has often been called simply "the medical model," of use for the subject I am addressing consist basically of two fundamental features not necessarily or logically connected but closely tied in practice for at least a century. The first is a particular scientific methodology, with a distinct approach to the body, a foundation in the biochemical sciences, and, most important here, a set of clinical techniques for determining the efficacy of specific treatments or procedures—in particular since at least the 1940s the clinical trial. The second is the dominance—that is, the quasimonopolistic power to define and implement scientific methodology—of a particular set of professions, above all mainstream doctors of medicine and allied practitioners, buttressed in most cases by the power of the state to license or refuse to license providers to practice.

Under this broad definition, alternative medicine would consist of any type of medical practice or theory that either challenges, or has in some manner been excluded from, one or both of these fundamental components of scientific medicine. Some forms of alternative medicine, such as faith healing, Christian Science, or homeopathy, challenge the methodology used by scientific medi-

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cine; others, such as chiropractic, challenge the power of particular types of providers to define that methodology and exclude them from it. Still others, of course, challenge both.

In practice, however, users of alternative medical procedures in the United States appear most commonly to seek not so much to overturn the medical model but to expand it more or less broadly by adding selected therapies and treatments to its methodology and (to a lesser extent) selected providers to those who control the system (4, 5). The considerable success of advocates for persons with AIDS in enlarging the accepted types of HIV therapies provides a particularly important example.

This expansionist aim implies that the boundaries between scientific medicine and alternative medicine are not fixed, but are socially and historically determined and depend to a large extent on the relative power of competing medical professionals. We need not reach back to the 19th and early 20th centuries to observe this fluidity in action (6); note the recent acceptance by the medical profession of certain elements once associated more exclusively with alternative medical approaches: a greater role for patients, the use of nutritional supplements, and a stronger emphasis on preventive care.

Another qualifier of the definition is that the abstract scientific model has, in practice, not always met its own supposed high standards of "scientificity." Power, social attitudes, and professional prejudice, for example, have played an important role in determining the content and practice of scientific medicine. In addition, much of what has been assumed to be anchored in clinical science has in fact never been tested and is—as we are now discovering, to our chagrin—based on little more than unproven, sometimes dangerous assumptions or simply the authority of physicians (7).

Most significant in some ways is the relatively wide and largely unavoidable divergence between the clinical sciences on which medicine is based and the everyday "art" of medicine as applied to individual patients in actual practice settings.

In spite of these problems and the relative imprecision of definitions and boundaries they reveal, the modern medical model is largely coherent, and its immense success as a general approach to healing can only be denied by those who are willfully blind. Precisely those impressive achievements help explain its symbiotic relationship to modern insurance and third-party payment systems.

Health Insurance and Third-Party Payment

All contemporary systems of third-party payment, no matter how much they differ in detail, evolved in the second and third quarters of this century for roughly the same reasons. Only then did the progress of scientific medicine, its modern forms of organization, and its ability to cure or ameliorate illness reach a level sufficient to convince governments, private financiers, and indeed whole societies, that access to medicine had become a necessity, something which should be spread as widely as possible among entire populations.

Medical care has always been relatively expensive and therefore not easy to obtain, and the need for it is differentially distributed within any population. Only a small proportion of the population in any given period accounts for most of the expenditure on medical care. In the United States in 1987 the top 1% of utilizers accounted for fully 30% of total medical costs, a concentration that has actually increased over time and continues to do so; in 1970, for example, the top 1% accounted for 26% (8). As a result of both cost and need, modern societies have deliberately created systems that increase the amount of financial resources available for medical care far beyond the level it might achieve in more ordinary commodity systems. In addition, the burden of the total cost of care has been spread broadly among the healthy majority and the relatively small minority of the sick.

Insurance as Part of Medical Model. Thus all contemporary third-party payment and insurance systems, including the United States systems (6, part II, Chap. 3; 9–11), grew up both as a response to the success of scientific medicine and as a crucial part of the methods by which medicine operated and achieved that success. Insurance systems are thus very much a part of the medical model. In the United States this intimate connection is reinforced by the fact that much of the insurance system was the direct product of physicians and hospital administrators seeking, first, to procure secure financing and, second, to keep the national health insurance systems emerging elsewhere at arm's length (9–11).

This insurer-provider relationship continues to mold the way in which U.S. insurance operates, reinforced by the tendency of the states to privilege the scientific medical professions over others through their powers of licensure, certification, and credentialing laws and regulations.

As systems that constrict or eliminate the operations of ordinary commodity markets, with in-

built financial constraints on consumption, all third-party payer arrangements are subject to immense pressures to expand medical care continually—indeed, beyond what the populations they cover can ultimately afford to pay for. Third-party payer arrangements, whether government or private, are basically social arrangements for the sharing of medical risk, and thus entail an obligation to the people served to constrain this tendency and to ensure that only useful medical care is provided and that costs are kept within society's and individuals' ability to pay. All third-party payer systems have found that the medical model offers, at least in principle and often in practice, a means of carrying out this obligation better than alternative systems.

The Concept of an Insurable Event. The medical model does this in two ways. First, and most importantly, it offers, virtually alone among competing medical systems, effective, scientific methods of testing the efficacy and appropriateness of medical procedures and treatments. Second, it offers a means of preventing the undermining of what is usually called in insurance terminology, "the insurable event." An event is normally thought of as insurable if it is not in the power of the insured person to determine its outcome. Medical events do not, strictly speaking, meet this definition, since so large a part of health care received is determined by patients themselves. However, under the medical model, physicians normally make the major decisions about the medical care individuals receive and, again at least in principle, do so based on scientific training and expertise. Professional dominance thus works toward preserving the concept of the insurable event, although in a somewhat attenuated form, since physicians have a stake in multiplying such events. In contrast to the medical model, many forms of alternative medicine stress individual patient autonomy and responsibility and often employ unlicensed and unregulated providers.

The Concept of Medical Necessity. These aspects of the medical model advantageous to the stability of third-party payers appear at their clearest in the crucial concept of "medical necessity," a principle that is central to modern insurance systems. Medical necessity is not easy to define and its specific content often varies from payer to payer (12), but it can be illustrated easily enough, using a contractual definition from one of the Empire Blue Cross and Blue Shield large-group policies:

The Health Care Plan will reimburse, according to the plan provisions, for Hospital, Surgical, Major Medical, and Den-

tal procedures and services provided that they are medically necessary. Medical necessity is determined by the plan administrator and insurance carrier. To be medically necessary, a procedure or service must be essential and indispensable for assuring the health of a patient; it must be generally accepted by the medical profession as required to diagnose or treat an illness or injury; it must be prescribed by a physician who is practicing within the scope of his or her practice and licenses; and it cannot be a service or procedure or level of care which is excluded from coverage by Plan provisions. The fact that a procedure, service, type or level of care is prescribed and/or administered by a physician or under the direction of a physician or other licensed medical practitioner does not necessarily mean that it is medically necessary and therefore covered by the Plan.

In other words, any particular procedure or pattern of treatment must have scientifically provable efficacy, be administered by medical professionals, and be subject to decision-making case by case and treatment by treatment. Reservation of the ultimate right of decision on medical necessity to payers themselves, a relatively new element evident in this quotation, is discussed below.

In all third-party payer systems, the range of what is considered medically necessary tends to change in the same ways as it does in the medical model. As new procedures or providers are brought within that model after proper testing and evaluation, they tend to become reimbursable by third-party payers. Thus, if specific types of alternative medicine seek to become part of the third-party reimbursement system, they have to become part of the medical model. To a limited degree and under certain conditions, some, such as chiropractic, acupuncture, biofeedback, and some forms of megavitamin and herbal therapy, already have. Survey data show that limited reimbursement for such alternative therapies appears to be available under certain conditions (4).

The need for participation in the medical model holds for third-party payment systems not only in the United States, but throughout the world. Third-party payer systems of the national health insurance type, notably in Canada, Great Britain, and Scandinavia, or of the largely private, mutual insurance type in place in Germany, France, Japan, and the Netherlands tend to use the same medical model and the same principles of medical necessity, with the same general results. Thus, altering the health care financing system appears, by itself, not to alter third-party payer attitudes toward alternative medicine.

Bringing Alternative Medicine into The Medical Model

How, then, can alternative treatments and procedures become part of the medical model and,

therefore, reimbursable under third-party payer arrangements? Several approaches, not equally successful, have been tried in recent years.

First, alternative providers and their patients or customers have applied considerable pressure directly on insurers and other third-party payers for inclusion. Although these efforts have had some successes, alternative medicines remain largely outside the scope of third-party payment. Payers are quite properly jealous of their prerogatives and cautious in adding new and potentially costly procedures to their lists of covered services.

Second, alternative providers and those who use their services have applied considerable pressure on state legislators and regulators to force third-party payers to include alternative treatments and therapies in their contracts. They have achieved somewhat greater success by this route, but government has largely been responsive to those forms of alternative medicine that most closely resemble in method and practice scientific medicine, such as chiropractic, acupuncture, or nurse-midwifery, and has often mandated the inclusion of specific alternative therapies, but only when provided by a medical doctor, not by an alternative therapist (13). Government appears to be almost as attentive to the virtues of the medical model as payers. Even courts are far more likely to force payers to cover experimental treatments that have not fully satisfied the requirements of the medical model than to cover specific forms of alternative medicine remaining outside the model entirely.

Scientific Testing. Potentially the best and in some ways the simplest means of achieving inclusion is through the use of scientific methodology itself. That is, many if not all alternative medical procedures and treatments can become subjects of clinical trials, literature reviews, and other scientific methods of testing for efficacy and appropriateness.

This is already happening with respect to some types of alternative medicine. The National Institutes of Health Office of Alternative Medicine is financing, among other things, studies of yoga for heroin addiction, acupuncture for depression, Chinese Qigong exercises for pain relief, hypnosis to help heal bone fractures, prayer to ameliorate illness, and mental imaging to help deal with asthma (14–17). Studies of varying quality have already been conducted with respect to homeopathy (18), and studies of the effectiveness of acupuncture and massage therapy for persons with AIDS are beginning, for example, at

Cook County Hospital and the Rush HIV Clinic in Chicago (19).

Finally, third-party payers are themselves beginning to design studies to test the efficacy of selected alternative therapies; one insurer, Mutual of Omaha, has already announced coverage for an alternative heart treatment consisting of a low-fat diet, meditation, yoga, and support groups instead of surgery or drug therapy (14–17). It is even possible that governmental or quasigovernmental bodies will ultimately become responsible for such testing and for determining what is reimbursable by all insurers. This procedure would eliminate the significant differences in approach both to scientific and alternative medicine among payers, at the same time rendering each individual reimbursement decision more momentous and more objective. The federal Agency for Health Care Policy and Research began issuing standard practice pattern guidelines in 1992 (20, 21). Individual states are moving in this direction as well: New York State created, as part of its renewal of its hospital reimbursement legislation at the end of 1993 (S6226/A 8936), a new State Task Force on Clinical Guidelines and Medical Technology Assessment, to begin the evaluation of clinical guidelines and technology assessment and to advise the governor and legislator on the specific role the state should take in these processes.

Several comments need to be made and caveats raised with respect to this trend. First, not all alternative therapies are equally testable using the medical model. Faith healing, for example, is surely more difficult to study than chiropractic. And although, in principle, the efficacy of particular herbs for medical purposes is no more difficult to test than, for example, any new pharmaceutical, testing would certainly be more difficult on herbalist approaches that argue not only that particular herbs have healing properties, but also that they do not work equally well for all individuals and that only the herbalist can decide which herb or combination of herb should be used for a particular patient.

Second, and following from this first point, what is normally being tested in the medical model is particular procedures and treatments, not entire philosophies or approaches to the human mind and body. The medical model can, for example, test the effects of acupuncture but not the Chinese philosophy on which it is based; it can test the efficacy of prayer but not the existence of a god or gods. Therefore, what is almost certain to happen is that specific alternative

treatments will be absorbed within the medical model, but not entire systems of therapy and their practitioners.

This leads directly to my third comment: medical practitioners and third-party payers may, in the future, be more open than in the past to alternative therapies, but they will absorb those therapies on their own terms. My own company, Empire Blue Cross and Blue Shield, does pay for chiropractic because its methodology is closely related to standard medicine; does pay for acupuncture but only when performed by a physician; and does pay for midwifery, but only for nurse-midwifery. In other words, alternative therapies will have to conform closely to the model of scientific medicine to become reimbursable under insurance contracts.

Unintended Effects of Inclusion. Not all alternative medicine therapists or their supporters will be happy with third-party payer reimbursement. Inclusion within the medical system will have a multitude of largely unintended effects on the nature and practice of alternative medicine, as inclusion has had on preventive medicine (22). Those for whom alternative medicine represents a direct challenge to the medical model would probably do better, I believe, not to press for reimbursement at all. The same is true for those who would make the individual consumer the sole judge of her or his medical needs. Such approaches will be systematically distorted by inclusion. Those who largely accept the medical model but desire that specific types of alternative providers, not merely alternative procedures, be included may be disappointed as well. Only those who, like the AIDs activists, mainly desire to expand access to potentially efficacious procedures and therapies within the medical model will be more or less contented.

Important Recent Developments

Two recent but crucial developments in the health field—the ever-present cost crisis, and the closely related shift in the locus of power in health care from providers to payers—will affect the question of third-party payment for alternative medicine.

Cost. Continual increases in the costs of medical care have certainly rendered all payers cautious about providing coverage for any new service, treatment, or technology, especially when expanding coverage for a new service is likely to mean less coverage for some other therapy (23).

We were told that covering home care for the

elderly and others would largely replace institutionalization and save significant sums of money, a claim that turned out to be false: home care is mostly additive, not substitutive (24–26). Also, we were told that preventive care would save millions of dollars in illness avoided, and that turns out to be equally dubious (27). Now we are being told that many alternative therapies will save payers large sums of money, since they are less costly than standard medical treatments, they focus on prevention rather than cure, and they would take the place of more expensive standard medical therapies (28). Insurers, quite rationally, will be skeptical of these claims in a world in which new therapies rarely save money at all; even now it is clear that alternative therapies are generally additive, not substitutive (1, 4, 28).

Covering a new service always seems to have a noticeable and undesirable effect on charges: they rise rapidly and steeply. The continuing cost crisis is not likely to make payers more inclined toward alternative therapies, except in those cases in which truly convincing evidence of cost effectiveness can be demonstrated.

Cost and Shift in Power from Providers to Payers. As medical costs rose steadily and uncontrollably during the 1970s, 1980s, and early 1990s, payers made substantial efforts to gain greater control over the entire system in order to reduce the rate of increase in their costs. Mainly they attempted to control medical utilization, turning to managed care and case management arrangements of all types, preauthorization reviews, and second-opinion programs. More recently they have embraced practice pattern guidelines, outcomes research and technology assessment, and normative comparisons of physician practice.

Although such approaches originated in the desire to gain control over systemic costs, they have had noticeable and probably largely unintended effects. They shifted power within the medical system away from physicians, the professionals traditionally in control of the system, and toward payers, traditionally mere conduits for passing money from groups of insured persons to providers of services. The insurer rather than the provider now has ultimate authority over medical necessity decisions in Empire's contracts, for example. Another shift of power has also taken place, this one among physicians—from the physician practicing in home or office to the health service researcher in research institutions, academic medical centers, and universities.

These developments mean that control of

medical decision-making has been altered significantly, and that payers are now increasingly dominant. As one physician observer has succinctly noted, "It is not stretching things too far to say that whoever controls practice policies controls medicine" (29). Payers have used their new power to alter medical methodology by insisting that medical science become more internally consistent, uniform, and rule-bound, and that its practitioners use only accepted, tested, and proven procedures and treatments. Stated differently, payers are forcing medical professionals to take more seriously their professed adherence to the method of scientific medicine.

Whatever one thinks of this development—and, on balance, I believe it is largely positive—it will have a significant effect on alternative medicine. As the medical model stresses scientific methodology to ever-greater degrees, alternative therapies and treatments will find becoming part of that model increasingly difficult. Therefore, it may be harder than ever for alternative methodologies to become reimbursable under insurance arrangements.

As the medical world changes dramatically, alternative therapies will become part of scientific medicine only slowly, if at all, and they will do so mainly by complying with the terms of the medical model and, in particular, on the terms laid down by the insurance and third-party payment systems that function as its financing arm.

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Science, Alternative Care, and Third-Party Payers

Moderator: DANIEL A. MOROS, PhD

Question: The deregulation of over-the-counter drugs as well as the unregulated alternative treatment programs in effect leave the responsibility for diagnosis and treatment up to the patient, whether the patient wants to accept it or not. Ironically, many people who advocate for the notion of empowerment do so without regard to the vital transfer of information. Providers of care must become much more responsive to consumers' needs and demands.

Question: I think it is no accident consumers find it far easier to get information about the performance and failure rates of the hard drives of their computers than about a physician who is going to be fiddling with your pancreas. The difficulty is not that individuals are just more gifted in seeing through these arcane matters of computer terminology but could not possibly understand, simple souls that they are, that—for example—40% of Dr. So-n-so's patients kicked the bucket within six months and only 3% of Dr. Thus-n-such's did. For reasons that suit the convenience of others, not patients, through legal canalization, restrictions on advertising, social pressures within a profession, individuals do not have information and cannot get it. Even if they invested a lot of time and energy trying to get it, they probably would not be able to, given the forces against them. If you want a competitive medical market place (and I am not weighing its prospects here), one of the things you have to do is not wait for competition to make information available to people.

Question: I think it is a false assumption that the use of placebos is largely a conscious and voluntary effort. It is actually an integral part of many medical treatments but it is done unknowingly. For example, there is the whole history of thousands upon thousands of medical administrations of drugs when very few of the drugs were in fact effective, or when inadequate doses were given, yet results were positive.

Question: Someone walking in wearing a white coat may already constitute a placebo effect. Suppose a mainstream doctor becomes aware of the fact that some of what he or she seems to be accomplishing is done through the placebo effect and is confronted with an interesting mental dilemma. One possible response is to think, "I have a tool I did not realize I had. The patient seems to be happier that I do this thing even though I now believe it is not part of my intervention, just a placebo effect." The physician uses it, maybe even better than before. Another response is, "Oh, my gosh! I thought that something had a specific action, but it turns out it is all placebo effect, and that is not scientific. I never want to do that again."

I think something in the spirit of scientific medicine says that the second response is the better one, and that some alternative healers—I express this to people who subconsciously describe themselves as "alternative healers"—agree. I am not sure exactly why. I think part of it is a question of values. There is a concrete question about public education and about the value of having people judge methods of reasoning on the basis of whether or not the science is there. The extent that people are encouraged by scientific doctors to embrace therapies that only work through the placebo effect undercuts the generally good thing of having people judge the therapies that are offered according to whether the science is there.

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And that is a reason for doctors not to use the placebo effect, even when they can.

Lina Shihabuddin: Let me add to that. First of all, we are equating what we do not know with what does not exist. We are assuming that when we give the patient sugar pills, nothing is happening. We do not know that. Maybe something is happening. When I, as a psychiatrist, talk to a patient for a whole week and then this patient is feeling better, something must be helping. His behavior is changing. Within the realm of behavioral medicine, we are hoping that one day we will be able to prove that we are changing the structure of the brain. There is some evidence that behavioral therapy and cognitive therapy do change the silicone concentration in the brain. So, if we are giving somebody a sugar pill, that does not necessarily mean we are not doing anything.

Question: Are any of you talking about the ethics of the role of the physician—what physicians can and cannot do properly, and what they can and cannot properly bill for? To some extent, you are suggesting that physicians are allowed to help people, but as doctors they are only supposed to do certain things in that role, and they are only supposed to bill for certain things in that role, and that is part of our whole understanding of the enterprise.

Question: Some of it is arbitrary, I think. My guess is that when patients come to a physician and are given pills, they think they have been given something that has a specific effect. If physicians are knowingly not doing that, they are giving something that is counter to what the patient came for, although if patients don't know the difference, they will probably go away happy. Then there is a side effect that I think is a general but still an important one: undercutting the general role of having people be critical and use appropriate standards that evaluate the therapies they are subjected to—putting your arm around pseudoscience and saying here, this will make you feel better.

Question: Is the determination of health versus disease less problematic in the case of, for example, the veterinarian treating livestock, where the "patients" are more or less property? It is easy to say that it is purely the functioning that I want out of this animal. Conversely, in the case of people going to the doctors and saying, I want this that or the other, is it more difficult?

Question: My own views on determinations of health in terms of objective factors about the functioning of an organism tend to be conserva-

tive and realistic. I think that it is basically the same question for chickens as for human beings. The fact that some group of psychiatrists claims that homosexuality is an illness, some also that it is not, and that God knows how many different syndromes are involved are all brought to insurers. Basically, we tend to call things diseases if we want to get insurance companies to pay for them, so there is a real interest in labelling some conditions a disease. The question of whether there is an objective basis to decide whether or not something is a disease is one question. It is quite another to ask what ought to be done in the case of particular individuals. For example, even though sterilization is a violation of species functioning, it is, as it were, a "disease," an impairment of function. If people want such an impairment of function, for the right reasons, that is their choice to make, is it not?

Question: The definition of disease is more difficult for humans, and some have tried to make plausible the argument that the definition of disease is independent even of the social conditions we live in. Thomas Szasz maintained that there is no such thing, objectively, as mental illness. What makes his views so unusual is that he goes further. He actually asserts that the notion of mental illness is completely naturalistic—part of the science of psychology that is not socially defined and doesn't need to be. He thinks we do not have an adequate theory of mental functioning but when we do, we will also have a theory that disease is completely objective.

Question: I think the special professional standards on the sufficiency and adequacy of evidence are the appropriate ones to apply for a lot of this kind of determination, but that does not help us understand the extended use of alternative therapies or the ways in which regular folks, by the millions, make those choices and find them satisfying and adequate.

Norman Gevitz: I organize the course "Realities of Medicine" at the University of Illinois College of Medicine. It involves 61 volunteer faculty members and has a number of parts, one called "alternative medicine," and each year we have an MD acupuncturist, someone who is board certified in internal medicine and who has given that up in order to practice traditional Chinese medicine. Each year he brings in patients of his, and there is a good interaction between the medical students and the patients, because the medical students learn why the patients go to this particular type of practitioner and what their stories are. In some humanities programs this idea is

now very popular—that is, to focus on narrative. What people's tales are.

What we see is a recurring history. For this particular physician and other unorthodox physicians in the course, a number of their patients go from doctor to doctor to seek out medical care. For one reason or another, they are dissatisfied with the type of care they are getting, and their standard of evidence is that they find relief. Basically, that is all they are interested in. Many of the patients actually say to the acupuncturist in the room, "I do not buy that theory at all, it does not make any sense to me, but it works!" and that is their standard of evidence.

It is very difficult for us on this discussion panel to say whether that is or should be the only important aspect in terms of such issues as reimbursement. William Fisk raised the issue that to learn, it is essential that we understand the stories of unorthodox practitioners. Not that we necessarily accept them, but that we listen to them, at least to come up with some kind of evaluation based on their perspective. To understand them better.

If medical students are to practice medicine, and 60 million people out there are using unorthodox remedies, they better know what is out there, why their patients are seeing those alternative practitioners. Paget, the orthopedic surgeon, a hundred years ago said to his orthopedic colleagues that if you do not learn the methods of the bone setters or learn about them, if one of them cures a case that you cannot, you have made a very successful competitor. To understand for the patients on welfare what is out there and to learn what perhaps might be useful, at least to examine it and to test it, is something that needs to be done in order to deal with the issue of unorthodox medicine on its own terms.

Question: On the question of well-being versus normal species functioning, consider the example that philosophers sometimes use to indicate that the satisfaction of what people want most is not necessarily what other individuals have to pay for. Somebody, for example, thinks that people should be provided with food if they are starving, and is faced with a person who would sacrifice nutritional well-being for the sake of building a monument to his God. His personal preference is to exchange food for this other thing which he values more, but that does not mean we have an obligation to pay for his food or to pay for those monuments to his God. The claim is that you cannot always deduce from someone preferring A rather than B that you have to provide them with

A rather than B, and you may still have an obligation to provide the B in some circumstances, even though they prefer to have A. I think that example is plausible.

Another point: some economists or political economists have been concerned with the standard of well-being or perceived well-being. There are a lot of people, for example, with undeveloped talents and people who typically set low goals for themselves, and they go around constantly saying, "I am fine, I do not need treatment" when they do have things objectively wrong with them. A standard of health and illness was set up at Harvard Medical School that did involve this subjective perceived well-being standard to counteract the consequence, in many circumstances where there are social inequalities, of not keeping up on the real illnesses that people have, because they have been conditioned to accept a lower standard of well-being for themselves.

Question: I imagine right now, in this city, there is a thriving market for food stamps where those who have them are trading them for the currency of the world with which they can invest in temples for their God or more likely chemical substances for their nose. It is very hard to prevent that sort of thing. Yet I think most of us would want, in our private charitable activity, to make that distinction. I might be willing to lend you five bucks to get you fed, but I am not going to pay five dollars so that you can dive into your drugs, and that is quite legitimate. It is very dicey when the state, which is supposed to be neutral toward the aspirations of the citizens, makes those sorts of determinations. I am not saying that it should not be done at all, at the level of the state, but I think, and minorities traditionally discriminated against know all too well, that when it comes to the preservation of neutrality, the state could be a lot better than its absence.

Question: If we accept the notion, and here is where the ideological battles begin, that there is some standard of health care we want everybody to have, because without that standard, the concept of citizenship, of a functioning society and functioning individuals is lost—if we accept that concept, then there are consequences to the choice we make of how to distribute health care. And it is not just public health. If I distribute health care in a purely private manner, purely according to the wishes of each individual, which is in a sense what we all profess to believe—we want to push the notion of private decisions and private welfare to its best—there will be serious economic and moral consequences on the nature of health

care. For one thing, you are going to have cost problems and, more importantly, you are going to have distribution problems. Some people are going to get more and some people are going to get less. That is precisely why we have third party payment systems all over the world, and why ours does not work very well—there are people left out of it. The system becomes distorted. We could argue whether the distortions that my particular socially oriented method of distribution creates are worse or better than the ones that yours create, but I think that the points of view should at least be clarified here.

Question: I think you have to be careful. We are

excluding these concepts in a self-protective way while just beginning to realize how prevalent they are. I do not think we should be attacking alternative therapy with such virulence. I think what we should be doing more of is asking why people are searching. What are we not providing them? What expectations do they have that are not being met? Otherwise, we will go the way of network TV—not thinking that cable with all its alternatives is going to be a threat. I think we need to look carefully at what we are not providing, not understanding. This is not to say that alternate therapy is always good, but what are we not providing with all our good science and high technology?

General Articles

Moses Maimonides:

Correcting Two Misconceptions

FRED ROSNER, M.D., F.A.C.P.

MOSES MAIMONIDES was Judaism's medieval giant, a man of unbelievable literary ability and encyclopedic knowledge. He mastered nearly everything known in the fields of theology, mathematics, law, philosophy, astronomy, ethics, and—of course—medicine. His first major work was his *Commentary on the Mishnah*, in which he wrote explanations, commentaries, and rabbinic rulings on all 63 tractates of the Talmud. His magnum opus is his *Mishneh Torah*, a monumental 14-book compilation of all biblical and talmudic law that remains a classic. His great philosophic masterpiece is his *Guide for the Perplexed*.

The purpose of this brief note is to correct two misconceptions about him: the year of his birth, and his putative authorship of the beautiful Physician's Prayer.

The Date of Maimonides' Birth. The nearly universal acceptance of 1135 as the year in which Moses Maimonides was born has recently been challenged. The controversy about the correct date should now be put to rest. The evidence that 1138 is the correct date is extremely convincing and nearly incontrovertible. It is based on at least two autograph manuscripts of his *Commentary on the Mishnah*, at the end of which the great sage clearly states that he was thirty years old when he completed his commentary in the year 1168 (1479 Sel.). Thus, he was born in the year 1138 CE.

The incorrect assumption that he was born in 1135 is based on several manuscript fragments

whose authors are unknown; these fragments perpetuated several errors and a confusion of dates from a single early manuscript. These errors and inconsistencies are detailed by several recent scholars, including Sassoon (1), Kapach (2), Kahana (3), and Havlin (4), who reject the suggestions by earlier writers that corrections of these "scribal errors" be made to fit the notion that Maimonides was born in 1135.

The words of Maimonides himself in his autographs are the strongest proof that 1138 was his birth year. The primary sources, early authentic manuscripts, are much more authoritative than the unclear, deficient fragments of later manuscripts written by unknown authors and full of errors and inconsistencies. These inconsistencies were perpetuated for centuries until Sassoon, Havlin, and Goitein (5) called attention to the autograph copy of Maimonides' *Commentary on the Mishnah*, and Kapach published a new Arabic edition and a Hebrew translation of additional autographic manuscripts of this commentary in which Maimonides states that he was thirty years old in the year 1168, when he completed his commentary.

The Authorship of the Physician's Prayer. The Physician's Prayer attributed to Moses Maimonides is a lofty and beautiful prayer which first appeared in print in a German periodical in 1783 (6). The anonymous prayer bears the title "Daily prayer of a physician before he visits his patients, from the Hebrew manuscript of a renowned Jewish physician in Egypt from the twelfth century." The first Hebrew version of the prayer was published by Euchel in 1790 (7). The title of Euchel's paper indicates that Marcus Herz was the author of the prayer: It was translated at his request from German into Hebrew. I have traced the various versions of the prayer that have appeared over the past two centuries in many languages

From the Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, New York, and the Department of Medicine, Mount Sinai School of Medicine (CUNY), New York, NY.

Address correspondence and reprint requests to Fred Rosner, M.D., Director, Department of Medicine, Mount Sinai Services at Queens Hospital Center, 82-68 164th Street, Jamaica, NY 11432.

and have provided additional evidence that the prayer was not composed by Maimonides and is falsely attributed to him (8).

Leibowitz points out that the style, phrasing, and concepts in the 1783 text of the prayer are not compatible with medieval authorship (9). A phrase such as "art is great, but the mind of man is ever expanding" is typical and characteristic of eighteenth-century Europe and is at variance with Maimonidean medieval thinking. Here, according to Leibowitz, is the idea of progress, which became even more popular in the nineteenth century. Further evidence for an eighteenth-century author lies in the phrase "act unceasingly and harmoniously to preserve the whole in all its beauty." This concept of "beauty," or *das Schöne*, is characteristic of German literature of the Enlightenment. Moreover, such a phrase as "ten thousand times in ten thousand organs hast Thou combined" presupposes knowledge of the newer sciences of anatomy, biology, and microscopy. The tensions between colleagues discussed in the prayer are also products of a more modern period and are dictated by the new academic hierarchy that arose in the eighteenth century. A number of other spurious works falsely attributed to Maimonides have recently been published in English (10–11).

The Physician's Prayer attributed to Maimonides contains moral and ethical standards by which physicians should conduct their professional lives. It is worthy of the lofty ideals and attitude toward the practice of medicine espoused by Maimonides. The healing of the sick, he states, is not only a moral and ethical imperative but is, in fact, a divine commandment. The daily recitation of this prayer serves to remind the physician to constantly embody the highest code of medical philanthropy and professional ethics.

Moses Maimonides is the most illustrious figure in Judaism in the post-talmudic era and one of the greatest of all times. He was famous as a

rabbi, philosopher, physician, legal codifier, theologian, astronomer, mathematician, and ethicist. As a physician, he treated disease by the scientific rather than the empiric method. His attitude toward the practice of medicine came from his deep religious background, which includes the divine commandment to restore health and preserve life. Sir William Osler called him "Prince of Physicians." Appreciation of his medical and other writings, now all available in English, has recently spread.

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Compensating Organ Donors and Jewish Law

FRED ROSNER, M.D., F.A.C.P.

THE SHORTFALL in the supply of organ donors for transplantation, always serious, has been growing for a number of reasons: increasing successes in organ transplantation, techniques for transplanting a new range of organs (pancreas, lungs, intestine, multiple organs such as heart-lung and kidney-pancreas, fetal tissues), an increased number of centers doing organ transplants, expanded criteria for determining recipient eligibility, and retransplantation requirements.

The need for organs is enormous. Over 60,000 people die annually or are maintained on suboptimal therapy who potentially could benefit from a kidney, heart, liver, heart-lung, pancreas, or lung transplantation (1). In spite of intensive efforts and major initiatives to increase the supply of organs, the number of donors available annually remains virtually unchanged.

Cash rewards for organs have been proposed in the United States although Congress banned the buying and selling of human organs with the 1984 National Organ Transplant Act. Although payment for organ donation is judged anathema by many people, a death benefit payment of \$1,000 has been suggested to motivate families of potential organ donors (2). Such a proposal, however, is considered by some to be "logically, ethically, and practically flawed," because payment undermines the altruistic consent process, encourages a black market of covert payments for organs, and raises the ethical issue of commodification of human organs, a slippery slope question (3).

Other suggested forms of monetary donor compensation include assistance in the payment of funeral expenses, a cash award to the estate of the donor, a cash award to a charity of the donor or the family's choice, or a limited low-cost life insurance policy redeemable on the donation of organs by the deceased policy holder (4). Concern has been expressed about the impact of financial incentives on the cost of already expensive transplant procedures (5).

Proponents of donor compensation point to the long-standing practice of payment for blood products, human sperm, and more recently, eggs (6) and surrogate motherhood (7). These are replenishable body products. Proponents of payments to donors of nonreplenishable organs such as kidneys also argue that the moral objections are overestimated and that the concern for the reversal of altruism is unfounded. Furthermore, it is morally wrong to let thousands of patients die for lack of donor organs (8). Certainly organs should not be placed on the block with bids and donations going to the highest bidder. But in a country such as India with no cadaver transplant program and where long-term dialysis is impracticable, there is no alternative for those with kidney failure but to "buy or die" (9).

The Structure of Jewish Law

The Pentateuch or Five Books of Moses is known as the Torah and is the fundamental source of all Jewish religious law. The Torah is sometimes referred to as the written or biblical law as opposed to the oral law, which represents the unwritten traditions which interpreted, applied, and supplemented the written Torah.

The widely accepted reduction to writing of the legal matter of the oral law is known as the Talmud, which consists of sixty-three tractates of

From the Departments of Medicine, Mount Sinai Services at Queens Hospital Center and the Mount Sinai School of Medicine. Address correspondence and reprint requests to Fred Rosner, M.D., Director, Department of Medicine, Mount Sinai Services at Queens Hospital Center, 82-68 164th Street, Jamaica, New York 11432.

opinions and teachings of many rabbis who analyzed, interpreted, dissected or commented on the written or biblical law. The Talmud was redacted and written by Rabbi Judah the Prince in the second century and completed by Rav Ashi in the fifth century.

Systematic codes of Jewish Law were written by Jewish scholars between the tenth and sixteenth centuries. The most famous are Moses Maimonides' (1138–1204) *Mishneh Torah* and Joseph Karo's (1488–1575) *Shulchan Aruch*.

The major rabbinic literature of the past four centuries consists of responsa, which are formal replies to legal queries addressed to rabbinic scholars of all generations. These responsa deal with social, political, and economic as well as legal problems and issues of their times. Hundreds of volumes of responsa have been authored by many rabbis over many centuries. This "case law" literature is part of the Jewish legal mainstream and serves as precedent authority for subsequent responsa.

The Jewish View on Organ Selling. The issue of payment for selling organs from living donors and from cadaveric donors involves different questions. These will be addressed in turn. The key questions are distinct and clear.

The Talmud states (10) that even if a man must sell the hair on his head in order to eat, he must hand over whatever real estate he has in order to pay the marriage settlement (*ketubah*) to the wife he is divorcing. None of the talmudic sages questions the legitimacy of such a sale. Elsewhere (11), it is related that the wife of Rabbi Akiba sold her hair braids to help support them. The removal of hair, however, involves no risk to the donor. Blood donation also involves no risk to the donor and is therefore permitted even if solely for the financial gain of the donor (12). Blood donation does not violate the prohibition against intentionally wounding oneself (13) since venipuncture is not considered to represent the infliction of a wound any more than is haircutting.

However, the donation by a live donor of any other organ, including bone marrow, of necessity involves anesthesia and surgery and hence is halachically classified as a wound. It is, therefore, not permitted solely for the financial gain of the donor. However, if the infliction of the wound is for the benefit of the health of the donor or the recipient, it may be permissible (14). Thus, to save the life of the recipient or to improve the health of the donor, the prohibition against intentionally wounding oneself is waived. Such "great need" makes permissible bone marrow, kidney, and other organ donation. Is it permissible, how-

ever, for the donor to be paid for an organ? Is the donor not morally obligated to donate a "spare" organ to save the life of another? The permissibility for a donor to undertake and undergo certain risks in donating an organ is discussed elsewhere (15). The majority of rabbinic responsa allow but do not require live donors to subject themselves to a small risk to save the life of a person dying of organ failure. But is payment permissible to the donor for that organ?

Prohibition on Receiving Payment for Fulfilling a Commandment (Mitzvah). In Jewish law, it is forbidden to receive financial compensation for fulfilling a commandment (*mitzvah*) or performing a meritorious act. Physicians, teachers, judges and their like are all considered to be fulfilling the biblical commandments of healing, teaching and judging and are thus not entitled to receive payment for their services. Jews must emulate G-d; just as He heals, teaches and judges without compensation, so must we.

The Codes of Jewish Law authored by Jacob ben Asher (1269–1343) (16) and Joseph Karo (17) rule that a physician is prohibited from accepting compensation for his medical expertise and knowledge but is allowed to receive payment for his trouble and his loss of time. In modern times, however, the concept of lost time needs to be re-examined. Physicians no longer derive their income from other endeavors as they did in ancient times.

In talmudic times, physicians, teachers (18), judges (19), and rabbis (20) were all categorized together as professionals who should not receive or accept compensation for their professional services. At that time, they could only receive payment for the interruption or time lost from their ordinary occupations to engage in their commanded activities. Nowadays, however, physicians, teachers, judges and rabbis have no other occupations, are therefore fully occupied with their professions, and are thus entitled to receive full compensation for their services. Is a person who fulfills the commandment of saving a life by donating an organ allowed to receive payment for that organ?

Payment for Organ Donation: Recent Rabbinic Rulings. It would seem that payment for organ donation in Judaism should not be allowed because the donor is performing a meritorious act or fulfilling a commandment (*mitzvah*). In fact, the opposite is true. There is no prohibition for the donor to receive financial compensation. Rabbi Mordechai Halperin offers several reasons for this conclusion (21). A physician is entitled to be compensated for this effort, time and expertise.

Similarly, an organ donor is allowed to receive payment for his pain and suffering in giving up his organ. A second reason is so as not to discourage organ donation. Finally, there is a great distinction between a physician who is biblically mandated to heal the sick and an organ donor who is allowed but not required to undertake the risks involved in organ donation. If the physician is allowed to receive compensation for his required services, certainly an organ donor is allowed to receive payment if he voluntarily chooses to donate. Halperin concludes that the general prohibition against receiving payment for the performance of a *mitzvah* does not in any way prevent the donor from requesting and receiving payment for his organ. The question of what constitutes a reasonable fee and what is an excessive fee is discussed elsewhere (22).

In his *Encyclopedia of Medical Ethics and Law* (23), Dr. Avraham Steinberg cites Rabbi Moshe Zev Zarger who rules that one should not take money for donating blood but if payment was agreed to in advance, it must be paid (24). Rabbi Moshe Feinstein permits a blood donor to receive compensation for his blood even though it is not needed urgently to save someone's life (25). His reasoning is based on the fact that the prohibition of intentionally wounding oneself is not involved since phlebotomy is essentially a painless and harmless procedure. Furthermore, bloodletting was practiced for centuries as a therapeutic measure. Hence there is no reason to prohibit it or to disallow a blood donor from asking for and receiving financial compensation.

Rabbi Moshe Tendler states that the Jewish point of view raises no objection to payment for organ donations and that a donor deserves remuneration for loss of earning power during the time in hospital (26). However, he expresses concern that remuneration not be used as a coercive force if great sums of money are offered.

Dr. Abraham S. Abraham quotes Rabbi Shlomo Zalman Auerbach who permits the payment of money to blood donors since the blood will be used for seriously ill patients (27). In regard to kidney donation, Abraham arrives at the same conclusion (28), namely payment to the donor is permissible. Since he has no absolute obligation to donate his kidney, he is entitled to compensation even if his entire motivation is for the money, because the recipient's life is prolonged by the transplant. Abraham again quotes Rabbi Auerbach who asserts that even if the donor is extremely poor or wishes to pay off his debts, since he knows that his donated kidney will benefit the recipient, the donor receives not only payment for

his kidney, but also full credit for having performed a meritorious act.

Selling Organs of Deceased People. Dr. Abraham raises the question about a deceased person whose relative seeks payment for giving permission to transplant the deceased person's kidneys or other organs into a needy recipient dying of organ failure (29). The issue involves the biblical prohibition against deriving benefit from the dead (30). Thus, it would seem at first that it is forbidden to receive payment for donating one's deceased relative's organs for transplantation. However, continues Abraham, if the money is to be used to save the life of another relative, it is permissible. Rabbi Auerbach is said to have agreed with the above.

Rabbi Eliezer Yehuda Waldenberg allows payment to relatives for the donation of the deceased's organs because the recipient's life would thereby be saved since the relative's consent is needed to provide the life-saving organ (31).

Furthermore, continues Waldenberg, for a variety of technical Jewish legal considerations, the prohibition against deriving benefit from the dead is not applicable.

Discussion and Conclusions

Organ transplantation in Judaism is a multifaceted topic involving many legal questions relating to the donor. The prohibitions on desecrating the dead, deriving benefit from the dead, delaying the burial of the dead and others are waived because of the overriding consideration of saving the life of the recipient. Other issues include the need (or lack thereof) for permission from the donor or next of kin for organ transplantation and the status of the donor buried without one or more of his "dead" organs now functioning in the recipient.

These questions have been answered in numerous writings on this subject (32–33). The conclusion of nearly all rabbinic decisors is that cadaver organ transplantation is permissible, desirable, and perhaps even mandatory to save the lives of people dying of organ failure, provided the donor is deceased at the time the organ is removed for transplantation. The present essay deals exclusively with the issue of payment to donors or their families for the organs. The rulings of most rabbinic decisors indicate that such financial compensation is permitted in Jewish law. However, a cadaver organ must not be withheld by the family because remuneration is refused or unavailable. The family has no "property rights" or estate rights to the body of their relative. It is

absolutely forbidden to let someone die because one receives no payment to save him. The Talmud clearly states "He who saves one life is as if he saved a whole world" (34).

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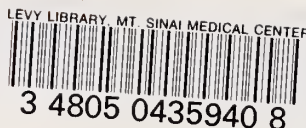
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Introduction

CHARLES D. GERSON, M.D.
Associate Clinical Professor
Department of Medicine
Mount Sinai School of Medicine

THE SUBJECT of diarrhea in immunocompetent individuals is extremely important as more and more people suffer from this kind of illness. Some of the factors contributing to that increase are:

- **International travel**, entailing the exposure of recently arrived immigrants and recently returned travelers to microorganisms and parasites not commonly encountered in the United States. More people are traveling to the Third World, and not all are taking the requisite precautions to protect their gastrointestinal tract. Illness often begins after the return home and is sometimes attributable to food ingested on the airplane. Although this type of illness is often self-limited, some bacterial and parasitic infections do require specific treatment.
- **Use and abuse of antibiotics**, which has undoubtedly changed in recent years. The spectrum of antibiotics available for treatment is wide, and physicians too often employ drugs that are stronger than necessary. In addition, antibiotics are often employed for illness that may not even be bacterial in origin. As a result the normal gut flora is altered, since many antibiotics have bacterial coverage that includes normal colonic organisms. The ecology of the gut is still largely unknown, but disequilibrating the gut flora not only has multiple metabolic effects, it also allows proliferation of pathogenic agents that may cause diarrhea.
- **The presence of achlorhydria**, which renders the host more susceptible to gastrointestinal infections. Acid secretion by the stomach is the first line of defense against orally ingested bacteria. In parts of the world where infectious diseases such as cholera and salmonellosis are endemic, individuals with achlorhydria have a significantly higher incidence of infection. Several populations in our own environment are at risk. In the elderly population, acid secretion is often reduced and sometimes absent. In nursing homes or hospitals, this group is particularly at risk. In addition, the use of potent antacid medications, especially omeprazole, has created a large group of patients with achlorhydria. The potential for gastrointestinal infection is increased in these individuals.
- **Impaired gastrointestinal motility** may also increase susceptibility; elderly people are one of the groups at risk. Many medications retard the normal peristaltic flow of intestinal contents. Since theoretically the struggle between host and infectious agent may be affected by bacterial adherence or intestinal clearance, motility appears to be another variable to be considered.
- **Improper handling and cooking of food** in restaurants, the proliferation of fast-food restaurants, and the urban practice of eating out or taking food home has also increased the incidence of infectious diarrhea. A glaring example is the occurrence of fatal infection with enterohemorrhagic *Escherichia coli* because of improperly cooked hamburger meat.

Research is actively being pursued in the areas of mechanism of infection, local and systemic immune factors, the molecular biology of bacterial adherence factors and mucosal binding sites, new forms of laboratory diagnosis, and new treatments. Discoveries of new infectious organisms, both bacterial and parasitic, have been and are continuing to be made.

Infectious Diarrhea in the Immuno- competent Individual

The three articles gathered here address an array of related issues: what tests to order, how far to go with studies of a patient who appears to have infectious diarrhea, when to treat, what is possible in the laboratory that can help the gastroenterologist, how to deal with antibiotic-associated *Clostridium difficile*, and what we should be thinking about in the returned traveler who has diarrhea.

First, Saul Agus discusses the approach in the office to a patient with infectious diarrhea. Edward Bottone describes the clinical, epidemiologic, and microbiologic correlates of definitive diagnosis, including what the clinician needs to tell the laboratorian, what tests are available, and how they should be used. Samuel Meyers discusses the diagnosis and treatment of diarrhea associated with *C. difficile* infection and antibiotic use.

This introduction by the guest editor is adapted from the panel discussion he moderated, "Gastrointestinal Infections in the Immunocompetent Individual," at the Mount Sinai Medical Center on May 5, 1994. Address reprint requests to the author at 80 Central Park West, New York, NY 10023.

Approach to a Patient with Infectious Diarrhea

SAUL G. AGUS, M.D.

AS A PRACTICING PHYSICIAN, I receive phone calls from patients who think they have food poisoning or gastroenteritis. The questions are which of these patients should be examined, what tests should be done, and what infections are likely to be found. My own daughter, a 20-year-old student living in a dormitory at a women's college in Manhattan, recently had severe abdominal pain, cramps, and diarrhea, and many of her friends were similarly affected. One of her friends was having bloody diarrhea, another was vomiting. In this group outbreak the infection turned out to be due to *Shigella*.

I think the most important thing from the clinical point of view in deciding how to approach the patient is the history itself. Some of these cases can be handled over the phone. Generally speaking, the body has a limited way of responding to a toxin, whether it is a preformed toxin, such as *Salmonella* or *Bacillus cereus*, or invasive gastroenteritis. The ways in which the body responds to the illness sometimes offer clues to the nature of the organism and to the severity of the illness.

Typical viral gastroenteritis, for instance, might begin with a viral prodrome, which I would describe as a viral express train going through the patient's system. Initial upper abdominal symptoms with nausea and vomiting are common, followed by the development of diarrhea. (I discuss some organisms that have the propensity to attack the small bowel below.) The differential diagnosis involves the distinction between a preformed toxin and an infection that develops within the patient. If it is a preformed toxin, the onset of symptoms is usually precipitous, and many persons probably have been exposed at the same time. Many of these preformed toxins, such as the staphylococcal enterotoxin, occur in warm weather when food sits around in picnic-type settings and can spoil. The toxin is preformed and ingested, and the onset of symptoms usually occurs within two to eight hours, often accompanied by vomiting, followed by diarrhea as well. Fever and systemic signs and symptoms tend not to occur.

In the case of bacterial infections by such organisms as *Salmonella*, *Shigella*, or *Campylobacter*, symptoms do not occur so immediately. A period of time must elapse while the organism proliferates within the body. The period is variable, depending on the size of the inoculum, the presence of risk factors such as the acidity of the stomach, motility factors, and the age of the patient. The period of development can be as short as 12 hours but is more likely to be 24 to 72 hours; in some slower-acting infections, as by *Giardia*,

Adapted from the panel discussion "Gastrointestinal Infections in the Immunocompetent Individual" at the Mount Sinai Medical Center on May 5, 1994. Final revision received Feb. 28, 1995. From the Department of Medicine, the Mount Sinai School of Medicine (CUNY). Address reprint requests to the author at 1080 Fifth Avenue, New York, NY 10128.

the period can be as long as one to two weeks. When the period is that long, the physician may not necessarily make the connection between the exposure and the actual event.

The symptoms themselves also vary. In an experimental setting at the National Institutes of Health, where we administered Norwalk agent to volunteers, I learned just how variable the symptoms can be in a range of normal individuals. Some normal individuals exposed to a defined toxin such as Norwalk agent will have no symptoms. Some will only vomit, some will vomit and have diarrhea, some will have diarrhea alone. One cannot predict exactly from the nature of the symptoms themselves what the invading organism is. To further complicate and confuse the issue, many of the mechanisms of diarrhea overlap. Some bacterial infections are invasive, producing a colitis-like picture. Some types of infections cause bleeding or stool that tests positive for blood, a typical example being *Shigella*. On the other hand, other bacterial infections, cholera for example, are characterized more by watery diarrhea and less by an outpouring of leukocytes. Some syndromes overlap, and a tremendous outpouring of fluid is accompanied by cramps and diarrhea as well.

Differential Diagnosis

In general, although not in all cases, I view the presence of vomiting and diarrhea at the same time as a good sign in deciding who has to be seen acutely and who can wait. Generally, the presence of vomiting and diarrhea is suggestive of gastroenteritis of some type. Obviously an early partial obstruction is also a possibility, but generally speaking, in a patient who is not immunocompromised, in a patient not suspected to have Crohn's disease or another underlying disease, simultaneous vomiting and diarrhea is generally a good sign, representing two of the body's mechanisms for clearing the toxin. Such symptoms often indicate self-limited disease. When the patient has only vomiting, the differential diagnosis is more complicated. There may be an obstruction or peptic ulcer disease.

When the patient has diarrhea alone, one has to think in terms of colitis, ileitis, and similar conditions. But in an otherwise healthy patient whose disorder has had an acute onset, gastroenteritis is likely to be self-limited. In most cases of amoebiasis, giardiasis, shigellosis, or salmonellosis, or infection by enteropathogenic *E. coli* or

Norwalk agent, the infection is self-limited, regardless of what the physician does.

Hydration. Only a small number of patients, those with intractable symptoms, need to be examined in the office. At this point, one has to evaluate the state of hydration of the patient. If the patient is well hydrated, the presumption is that generally speaking the problem is not a cholera-like mechanism of an outpouring of fluid but a more colitic-like disorder.

Fever. The presence or absence of fever may or may not be helpful in diagnosis. The physical signs are usually nonspecific.

Appendicitis. An important question in differential diagnosis—possible appendicitis—arises when confronting a patient who has diarrhea and right lower quadrant pain. This question is especially relevant in *Yersinia* infections, and sometimes in *Campylobacter* infection, which can simulate the signs and symptoms of appendicitis. One is partially reassured if there is tenderness in many spots, and if there is no focal rebound.

Group Outbreak. One is reassured to some extent if other individuals in the same setting have similar symptoms. My own records for the past month reveal infections even in people living in the greater New York region who have not left the United States and who have taken most of their meals at home. Three members of one family had a typical *Campylobacter* infection. Another family had *Giardia* infection.

Rectal Bleeding. The next differential point is whether or not there is any rectal bleeding. If there is blood in the stool, it behooves the physician to investigate in the office setting, at the time of examination, usually in the form of a limited sigmoidoscopy, which to me nowadays means using a flexible sigmoidoscope. An anoscope is usually not enough, because it does not go high enough to appreciate the rectal mucosa. A full colonoscopy is probably too invasive and a rigid sigmoidoscope is passé. But a flexible sigmoidoscope, generally speaking, even in the unprepared patient, can yield the best information. Specifically, the physician would look for an entirely normal colon, which is reassuring, with hemorrhoids that could be the cause of the bleeding. A diffuse pattern of infections suggestive of an infectious gastroenteritis might be revealed. A diagnosis of acute ulcerative colitis might be made. It is not uncommon to unexpectedly identify pseudomembranous colitis as well, which is definitive and often does not even require laboratory confirmation; treatment can be initiated immediately.

Obtaining Cultures. I do not necessarily take cultures from all individuals, but I certainly do so in those individuals who are sick, who are febrile, or who have abdominal pain and tenderness. I also take cultures in the office setting at the time of initiation of treatment, knowing full well, however, that in many cases, say infection with enteropathogenic *E. coli*, we are not going to get a positive result with the kinds of routine cultures that we do. Laboratories have to be alerted to infections with *Yersinia* and *Campylobacter*.

Summary. From the practical point of view, the differential diagnosis depends on the following factors:

- duration of illness
- sickness of the patient
- presence or absence of fever
- finding of abdominal tenderness
- presence of rectal bleeding
- age of the patient
- patient's state of hydration

Bacterial Gastroenteritis:

Microbiologic, Clinical, and Epidemiologic Correlates in Diagnosis

EDWARD J. BOTTONE, PH.D.

THE GLOBAL IMPACT of gastrointestinal disease, especially among children under 5 years of age, is striking; the number of deaths approaches 5 million annually in some Third World countries in Africa, Asia (excluding China), and Latin America, and, for survivors, secondary sequelae—growth retardation and severe malnutrition—are significant (1). In this presentation of a microbiologist's perspective on gastroenteritis I review the information needed to make a definitive microbiologic diagnosis.

Expansion in Number of Causative Bacteria

The number of bacterial agents recognized as causing gastroenteritis has expanded greatly since I first began my work in microbiology some 35 years ago. At that time one searched for the classic diarrheagenic agents such as *Vibrio cholerae*, *Salmonella*, and *Shigella*. Then came recognition of the role of enteropathogenic *Escherichia coli* (EPEC) in neonatal diarrhea, and we sought *Staphylococcus aureus* as a putative agent of enterocolitis. Concomitant with the introduction of methods to assess for bacterial virulence factors came an increase in the number of species recognized as enteropathogens (Table 1). Among the gram-negative species, *Campylobacter*, *V. parahemolyticus*, the enterotoxigenic *E. coli* (ETEC), and those that produce a heat-labile (LT)

cholera-like toxin and a heat-stable (ST) toxin were defined. With the recognition of enteroinvasive *E. coli* (EIEC) came the awareness that, clinically, such strains produce a disease indistinguishable from that caused by *Shigella* (2). More recently, the enterohemorrhagic *E. coli* (EHEC), which produce a shiga-like cytotoxin, have been associated with major outbreaks of hemorrhagic colitis and the secondary sequelae of hemolytic uremic syndrome (3). In the United States, *Yersinia enterocolitica*, serogroup 0:3, emerged as a primary cause of gastroenteritis, particularly among infants and children (4), and was followed by the carefully honed elucidation of *Aeromonas* species, especially *A. caviae*, as enteropathogens in pediatric (5) and adult patients.

Non-01 serogroups of *Vibrio cholerae* have long been thought to be of little clinical significance, yet toxin-producing strains of serogroup 0139 *V. cholerae* have clearly been associated with gastroenteritis (6), as have about 10 additional non-cholera-causing species of *Vibrio* (7). Obviously, as this list of recognized bacterial enteropathogens grows, one begins to wonder what flora are "normal" in the gastrointestinal tract. For instance, although enterotoxigenic *Klebsiella pneumoniae* (8), *Citrobacter freundii* (9), *Enterobacter* species, and *Bacteroides fragilis* (10) have been described, no attempt is made in the bacteriology laboratory to search for and distinguish such species to establish their etiologic role in any given episode of gastroenteritis.

Similarly, we may ask what the role of the highly invasive *Listeria monocytogenes* is in the gastrointestinal tract. Does it produce an enteritis subsequent to ingestion in contaminated foods (11)? What about *Pseudomonas aeruginosa*? There are reports of this microorganism producing an enterotoxin (12), yet neither this species

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nor *L. monocytogenes* is accorded any special consideration in studies of a stool specimen for enteropathogens.

The setting of human immunodeficiency virus infection has spawned, in addition to the agents mentioned above, a plethora of bacterial, fungal, mycobacterial, protozoal, and viral agents of gastroenteritis to which clinicians and microbiologists must devote their diagnostic talents. Certainly, prior to HIV infection few, if any, stool specimens were processed for the visualization or recovery of *Mycobacterium avium-intracellulare* (13), *Cryptosporidium* species (14), *Microsporidium* (15), and blue-green algae (*Cyclospora* species) (16).

Diagnosis of Diarrheal Illness

The diagnosis of an infectious diarrheal disease of bacterial etiology entails four cardinal points: provision by the clinician of epidemiologic information, indication by the clinician of the clinical syndrome (for example, watery or bloody diarrhea), selection of appropriate media for the putative pathogen, and assessment for virulence factors of an isolate when the species designation is not synonymous with pathogenicity. For instance, if one isolates a *Salmonella* or *Shigella* species from the stools of a symptomatic patient, its significance is accepted. However, in the case of *E. coli*, unless virulence factors (enterotoxin production, enteroinvasiveness) are determined, the isolate is regarded as part of "normal flora." In the case of *Yersinia enterocolitica*, interpretation and hence significance revolves around serogroup designation and biochemical profile (17).

Epidemiologic Information. The relevant epidemiologic information aiding diagnosis covers such questions as whether the patient is one among others in an outbreak of group infection or has consumed any particular food that may have been linked to an outbreak—chitterlings with *Y. enterocolitica* (18), seafood with a *Vibrio* species, poultry with *Salmonella* (19) or *Campylobacter* (20). Climate and time of year are relevant; for example, there is a dramatic increase in *Aeromonas* infections during warmer months, concomitant with an increase in the use of recreational water facilities (21). Was the patient housed in a day-care center or nursing home, or is the patient part of a unique population, such as campers? Any epidemiologic insight that can guide the laboratorian's efforts in the selection of appropriate media and incubation conditions should be noted on the clinician's requisition slip.

Clinical Picture. Clinically, although overlapping presentations may occur, enteric infec-

TABLE 1
Gram-Negative and Gram-Positive Bacterial Species Linked to Gastrointestinal Tract Infection

Family and genus	Species
Gram-Negative	
Family Vibrionaceae	
Genus <i>Vibrio</i>	<i>V. cholerae</i> <i>V. parahaemolyticus</i>
Genus <i>Aeromonas</i>	<i>A. hydrophila</i> <i>A. sobria</i> <i>A. caviae</i>
Genus <i>Plesiomonas</i>	<i>P. shigelloides</i>
Family Enterobacteriaceae	
Genus <i>Escherichia</i>	<i>E. coli</i>
Genus <i>Shigella</i>	<i>S. dysenteriae</i> <i>S. flexneri</i> <i>S. sonnei</i> <i>S. boydii</i>
Genus <i>Salmonella</i>	<i>S. typhi</i> <i>S. paratyphi A</i> <i>S. choleraesuis</i> <i>S. enteritidis</i> var. <i>typhimurium</i> (1500 varieties)
Genus <i>Yersinia</i>	<i>Y. enterocolitica</i> <i>Y. pseudotuberculosis</i>
Family Spirillaceae	
Genus <i>Campylobacter</i>	<i>C. fetus</i> spp. <i>jejuni</i>
Family Bacteroidaceae	
Genus <i>Bacteroides</i>	<i>B. fragilis</i>
Gram-Positive	
Family Bacillaceae	
Genus <i>Bacillus</i>	<i>B. cereus</i>
Genus <i>Clostridium</i>	<i>C. difficile</i> <i>C. perfringens</i>
Family Micrococcaceae	
Genus <i>Staphylococcus</i>	<i>S. aureus</i>

tions may be regarded as luminal, mucosal, and penetrating or systemic (Table 2). In many instances the clinical picture portrays the virulence factors produced by the enteropathogen. For instance, purely enterotoxigenic species such as *V. cholerae* and enterotoxigenic *E. coli* (ETEC) produce a fluid-secreting (cytotoxic) toxin, whereas enterohemorrhagic *E. coli* (EHEC) and *Clostridium difficile* produce a cytotoxic enterotoxin, which gives rise to bloody diarrhea with inflammatory changes occasioned by pseudomembranes and plaques visible on endoscopy (*C. difficile*). Such a clinical picture, although enterotoxin-mediated, mimics that produced by an enteroinvasive species (Table 2).

The major site of expression of enterotoxin production is the small bowel, whereas enteroinvasiveness usually occurs in the colon. Because invasive species such as *Salmonella*, *Shigella*, en-

TABLE 2
Clinical Symptoms of Infectious Diarrhea by Causative Species

Site	Symptoms	Species
Luminal Small bowel	Noninflammatory watery diarrhea	Toxigenic: <i>Vibrio cholerae</i> enterotoxigenic <i>Escherichia coli</i> (ETEC) <i>Staphylococcus aureus</i> <i>Clostridium perfringens</i> <i>Bacillus cereus</i> enteroadherent <i>Escherichia coli</i> (EAEC)? <i>Aeromonas</i> sp Early phase <i>Salmonella</i> , <i>Shigella</i> , <i>Campylobacter</i> infection
Mucosal Distal small bowel, colon	Inflammatory dysentery, blood, mucus, fecal leukocytes, fever	Enteroinvasive-cytotoxigenic: <i>Shigella</i> spp enteroinvasive <i>Escherichia coli</i> (EIEC) <i>Campylobacter jejuni</i> <i>Salmonella</i> <i>Yersinia enterocolitica</i> <i>Clostridium difficile</i> enterohemorrhagic <i>Escherichia coli</i> (EHEC)
Penetrating Systemic Invasive	Diarrhea infrequent Pain right lower quadrant Bacteremia	<i>Salmonella typhi</i> <i>Yersinia enterocolitica</i> <i>Yersinia pseudotuberculosis</i> <i>Listeria monocytogenes</i> ?
Colonic ulcerations	Pseudomembranes and plaques on endoscopy	<i>Clostridium difficile</i>

teroinvasive *E. coli* (EIEC), and *Campylobacter* are enterotoxigenic as well, watery diarrhea may be an early expression of the bacterial pathogen.

Species with a greater propensity for invading the gastrointestinal tract often produce a bacteremic disease in the appropriate host. For instance, *S. typhi*, the agent of typhoid (enteric) fever, produces bacteremia in normal hosts, whereas *Y. enterocolitica* usually produces bacteremia in immunocompromised hosts or those with some underlying disease or iron overload (22). Both, however, can produce severe local manifestations, such as terminal ileitis or mesenteric lymphadenitis. Again I raise for consideration *Listeria monocytogenes*, whose main clinical presentation is bacteremia and meningitis primarily in immunosuppressed hosts. Does this bacterium have an infectious component in the gastrointestinal tract?

Laboratory Diagnosis. Although the majority of diarrheal episodes are self-limiting, and most noninflammatory episodes respond to rehydration therapy, persistent or severe diarrheal illness may necessitate laboratory assistance in the microbiologic evaluation of a stool specimen. In some instances, a colonic or upper intestinal tract biopsy may also be necessary to establish a diagnosis.

In the laboratory, stool specimens may be examined grossly and microscopically, and portions

containing blood or mucus preferentially examined and cultured. Microscopically, the presence of blood and polymorphonuclear leukocytes is suggestive of an invasive organism (23), especially *Shigella* species (24), whereas an inflammatory response is absent in the stools of patients with fluid-secreting diarrhea. Mononuclear cells may predominate in the stools of patients with *S. typhi* infection.

The preponderance of one type of microorganism in a Gram-stained smear of a fecal specimen, such as staphylococci, gram-positive rods suggesting *Clostridium*, or gram-negative curved and "seagull-like" rods indicative of *Vibrio* or *Campylobacter*, may suggest the presence of a specific enteropathogen. A wet mount of the specimen is also valuable because the observance of rapid, darting motility may signal *Campylobacter*, *Vibrio*, or *Aeromonas* species; numerous nonmotile rods embedded in a meshwork of mucus and leukocytes may indicate *Shigella*. These observations, although not definitive, can be helpful in the selection of appropriate culture media and may even suggest a therapeutic approach prior to definitive results of culture.

The successful recovery of a bacterial enteropathogen requires a good working knowledge of the available "enteric" media and the colony characteristics of pathogenic species on these media. In concert with epidemiologic correlates, mi-

TABLE 3

Methods for Detecting Virulence Factors of Enteric Pathogens

Method	Virulence factor assessed
Tissue culture	Adherence, invasiveness, enterotoxins
Immunology	Enterotoxin (<i>C. difficile</i>)
Latex agglutination	Shiga toxin
ELISA	Cholera toxin
Animal models	
Ileal loop	Cytotoxic heat labile (LT) enterotoxins
Suckling mouse	Cytotoxic heat stable (ST)
Infant rabbit	Cytotoxic enterotoxin (<i>B. fragilis</i>)
Molecular biology	
Nucleic acid probes	Heat stable, heat labile enterotoxins Adhesin and invasion plasmids Toxin converting bacteriophages
Polymerase chain reaction	Enterotoxigenic <i>E. coli</i> LT gene Shiga toxin genes in <i>E. coli</i>

croscopy, and so on, definitive media for a select bacterial pathogen may be chosen. These include Campy agar (*C. jejuni*), thiosulfate citrate bile sucrose agar (*Vibrio* species), cefsulodin-irgasin-nalidixic acid agar (*Y. enterocolitica*), and MacConkey-sorbitol agar (enterohemorrhagic *E. coli*), to name a few. During warmer seasons it may be useful to inoculate fecal specimens to blood agar, which may facilitate the recovery of *A. hydrophila*, many strains of which produce colonies surrounded by a zone of β hemolysis. Incubation temperatures of inoculated media should reflect the temperature advantage for recovery, such as 42°C for *C. jejuni*, 25°C for *Y. enterocolitica*.

Special Procedures. In difficult cases or even in exceptional cases, a variety of special procedures has been used to detect an enteropathogen, especially *S. typhi*. Included among these is the detection by latex agglutination of *Salmonella* and *Shigella* antigens in stool specimens enriched in broth prior to culture to agar media (25) and the use of the "string test" (string capsule device) for the recovery of *S. typhi* from the small bowel (26). Earlier diagnosis of *S. typhi* infections has also been attempted through culture of the mononuclear cell-platelet fraction of blood (27). Serologically, the "febrile agglutination" test has been made more specific by the detection in human sera of an IgM antibody response to a 52 kDa protein of *S. typhi* (28). Additionally, through the use of monoclonal antibodies, *S. typhi* lipopolysaccharide "O" antigen 9, which is different from the

52 kDa protein, can be detected in urine and plasma samples of patients with typhoid fever (29).

Determination of Virulence Factors. The diagnosis of a diarrheal illness of bacterial origin requires the isolation and identification of the suspected pathogen. Additionally, for species such as *E. coli* that can be "normal flora," it may become important to assess an individual isolate for virulence traits such as enteroinvasiveness, enteroadherence, and cytotoxic or cytotoxic enterotoxin production (Table 3).

Many molecular biology techniques have been developed to detect genes encoding virulence traits and enterotoxin production (Table 3). Most of these technologies are still experimental, and hence have not yet made their way into routine use in the clinical microbiology laboratory. Their application has recently been reviewed (30).

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Treatment of *Clostridium difficile* Infection

SAMUEL MEYERS, M.D.

CLOSTRIDIUM DIFFICILE is the agent that causes pseudomembranous colitis associated with antibiotic therapy. The typical features of *C. difficile* infection vary from asymptomatic carriage to severe, toxic megacolon, which may be complicated by perforation (1). The most severe cases are luckily the least common.

A patient with mild *C. difficile* infection has diarrhea, sometimes accompanied by cramping lower abdominal pain. Symptoms usually occur during or shortly after antibiotic use, but may be delayed for weeks. Physical findings are usually normal; mild lower abdominal tenderness may be noted. In these cases endoscopic findings are usually normal.

Severe colitis without pseudomembrane formation may produce profuse diarrhea, abdominal pain, and distention. There may also be fever, anorexia, malaise, and dehydration. Peripheral blood leukocytosis is common. Fecal leukocytes and occult gastrointestinal blood may be present, but frank hematochezia is rare. Endoscopy reveals diffuse or patchy colitis.

Pseudomembranous colitis is the most dramatic presentation of *C. difficile* infection. The clinical picture is similar to that in non-pseudomembranous colitis except that intestinal and systemic symptoms are more severe. Endoscopy shows the typical adherent yellow plaques that vary in diameter from 2 mm to 10 mm. The intervening mucosa typically appears normal or

only mildly erythematous. In some cases, the plaques may coalesce to cover large areas of the mucosa. The rectum and sigmoid are typically involved; however, in 10% of patients the disease is confined to the proximal colon. In these latter cases, sigmoidoscopy may be inadequate to verify the diagnosis. If the disease progresses to fulminant colitis, the patients become acutely ill with lethargy, fever, tachycardia, and abdominal pain. Occasionally, megacolon is revealed on abdominal radiograph.

Almost every antibiotic has been implicated in the etiology of *C. difficile* infection. Clindamycin, ampicillin, amoxicillin, and the cephalosporins are the most commonly associated, the aminoglycosides, bacitracin, metronidazole, and vancomycin among the least common (2). Every time an antibiotic is prescribed there is a definite risk. If the antibiotic is given, the benefit must be sufficient to outweigh the risk.

Diagnosis

In both infants and adults, *C. difficile* infection is generally acquired in a hospital setting, although it can occur in the community. Hospitalized patients are the primary target because they receive antibiotic therapy in a setting where environmental contamination with *C. difficile* spores is commonplace (3–6). Neonatal colonization is common, but almost invariably asymptomatic, despite stool cytotoxin levels that may be similar to those in adults with severe colitis (7).

The laboratory diagnosis depends on the demonstration of *C. difficile* toxins in the stool. The stool-cytotoxin test is a tissue-culture assay based on the induction of cell rounding by the *C. difficile* toxin B in stool filtrate. This assay is the gold standard because of its high sensitivity (94%–100%) and specificity (99%) (8, 9). A stool

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culture for *C. difficile* organism is a less efficient method for establishing a laboratory diagnosis. The identification rate is less than for the toxin, and some strains identified are nontoxigenic (10).

Several rapid immunoassays for the detection of *C. difficile* antigens or toxins are now available. The latex-agglutination test is widely used, but has poor sensitivity (48%–59%) and specificity (95%–96%). This test was designed to detect toxin A of *C. difficile*, but instead identifies another bacterial protein present in nonpathogenic strains of *C. difficile* and other nonpathogenic clostridia (11). More recently, several enzyme immunoassays have been introduced that measure *C. difficile* toxin A or B in stool samples and have good sensitivity (69%–87%) and specificity (99%–100%) (8, 9, 12).

The stool-cytotoxin test is the most sensitive and specific assay available. However, it is expensive and requires the overnight incubation of samples. The enzyme immunoassays are quicker, require less specialized laboratory personnel, and provide reasonable sensitivity and specificity at a lower cost. The latex agglutination test is not recommended. It is important for clinicians to be aware of which assay is performed by their laboratory. Ideally, they should have both the cytotoxin and enzyme immunoassay available and be able to select the appropriate test for each individual patient. We must remember that no assay is completely accurate. If the clinical pattern is suggestive of *C. difficile* colitis, this diagnosis should be pursued even if the initial toxin assay is negative. Although endoscopy is a useful diagnostic tool, it is in these problem cases that sigmoidoscopy or colonoscopy are especially helpful.

Treatment

The simplest therapeutic step is to discontinue the offending antibiotic. If this is not possible, use an agent that is infrequently associated with this complication, while giving oral vancomycin. Supportive measures should be immediately implemented. Since the infection is nosocomial, measures that prevent cross-infection are recommended. These include enteric isolation, the use of disposable gloves, hand washing in a suitable disinfectant, the use of single-use thermometers, and environmental disinfection with agents that destroy the *C. difficile* spores (5, 13, 14). The same measures that apply to a hospitalized patient should apply to a patient treated at home.

Oral metronidazole (250 mg, four times daily) and oral vancomycin (125 mg, four times

daily) are equally effective in treating diarrhea caused by *C. difficile* infection (15, 16). Symptomatic improvement can be expected within 72 hours, and diarrhea and colitis resolve completely in more than 95% of patients after ten days of therapy.

Oral vancomycin therapy destroys *C. difficile* without being appreciably absorbed or metabolized. It is excreted unchanged in the stool and has minimal adverse effects. Metronidazole has several disadvantages when compared to vancomycin. Since it is readily absorbed in the upper gastrointestinal tract, systemic side effects are more likely to occur. Metronidazole-resistant strains of *C. difficile* have been isolated, and there are even reports of diarrhea induced by metronidazole. Despite these disadvantages, metronidazole has the one important advantage of a much lower cost than vancomycin (16, 17). The choice of agents must be individualized for each patient. I usually suggest vancomycin for the sicker patient. In this circumstance, I want every assurance of a good clinical response with minimal side effects.

Patients who cannot tolerate oral medication can be treated with intravenous metronidazole. Excretion of the drug into bile and exudation from the inflamed colon into the gastrointestinal lumen result in bactericidal levels in the feces (18). Similar excretion of oral vancomycin into the gastrointestinal tract has not been demonstrated (18).

Bacitracin is active against *C. difficile* and is minimally absorbed in the gastrointestinal tract. However, it is expensive and is less effective than vancomycin or metronidazole (15). It is therefore not a first-line therapy for the treatment of *C. difficile* infection. Cholestyramine may act as a resin to absorb the toxin and has been used for therapy. The response rate of 68% is the lowest of the agents discussed (15).

Inflammatory Bowel Disease

There has been controversy regarding the appearance of *C. difficile* infection in patients with inflammatory bowel disease. Several reports have specifically commented on the absence of *C. difficile* organism and toxin in these patients (19, 20). However, others have suggested an important association, both with and without recent antibiotic exposure (21–23). Toxin-induced mucosal injury has been postulated as a contributory factor in the underlying bowel disease. This concept was supported by clinical improvement concomitant with toxin disappearance, either spontane-

ously or with specific therapy (21–23). At The Mount Sinai Hospital, we demonstrated the *C. difficile* toxin in the stool of 3 of 18 patients with ulcerative colitis and 1 of 26 with Crohn's disease (24). Each of our patients with demonstrable toxin had received antibiotics at the time of study or within the prior two months. There was no apparent relationship between the appearance of the toxin in the stool and the severity, extent, or duration of the inflammatory bowel disease.

Our data are in contrast to reports of the presence of *C. difficile* toxin without antibiotic exposure. The discrepancy may be explained by deficiencies in the latter studies, in many of which only limited information was available on the antibiotic use of the patients studied. Some of those patients had concomitant abnormalities, such as subtle ileostomy dysfunction with intestinal obstruction, which can result in *C. difficile* infection without antibiotic exposure. Also, the possibility of nosocomial infection was not considered.

In summary, I agree that *C. difficile* toxin may occur in the stool of patients with inflammatory bowel disease. Such occurrences are usually related to antibiotic exposure, although other rare causes may exist. Despite the potential for colonic injury, the presence of the toxin is unlikely to be a common, significant, contributory factor in the underlying inflammatory bowel disease. However, there are circumstances in which the detection and therapy of *C. difficile* infection may be important. One such circumstance would be a patient with recent antibiotic exposure or with a potential nosocomial infection, especially if he or she is not responding to the usual therapy. A patient with ileitis or ileocolitis being treated with an antibiotic who suddenly develops a new or extended colitis is likely to have *C. difficile* infection.

Treatment of Recurrent Infection

The relapse rate after successful therapy of *C. difficile* infection can be as high as 20% (25). Some patients may relapse many times. Mild symptomatic relapses may respond to discontinuation of the antibiotic or a change to one less likely to cause *C. difficile* infection. Specific therapy is required for more severe or persistent cases. A variety of drug regimens have been suggested for these patients (26). Oral vancomycin or metronidazole therapy may be repeated one or more times. There is no clear rationale for switching medications, since the development of antibiotic resistance is not usually the cause of relapse.

When repeating the therapy fails, combination therapy with vancomycin and rifampin has been suggested. Others use vancomycin or metronidazole, followed by three weeks of treatment with cholestyramine or cholestyramine plus lactobacillus. Prolonged low daily doses, alternate-day doses, or slowly tapering doses of vancomycin may also be useful. Less conventional therapies include bacteriotherapy with fecal enemas and the administration of nontoxigenic *C. difficile* (27, 28).

Saccharomyces boulardii is a nonpathogenic yeast which is widely available in Europe. Oral administration has been shown to reduce the incidence of antibiotic-associated diarrhea in hospitalized patients (29). *S. boulardii* has also been found to be useful for treating relapsing disease (30, 31). The only side effects have been abdominal bloating and large bulky stools in some patients. This yeast has great promise in the therapy of *C. difficile* infection, despite the fact that the mechanism of its action remains unknown.

Immunocompetence and Infection

Systemic and mucosal antibody responses to the *C. difficile* organism and toxin may play a role in host susceptibility to, or clinical manifestation of, *C. difficile* infection. This role may be especially important in patients who are difficult to treat and have frequent relapses. This concept was suggested by the finding that *C. difficile* infection is more common among children with hypogammaglobulinemia than among normal individuals (32). Moreover, children with chronic relapsing *C. difficile* colitis with low levels of anti-toxin A IgG have shown both clinical and microbiologic responses and increased levels of anti-toxin A IgG after treatment with intravenous gammaglobulin (33).

A similar situation exists for adults. The mean serum immunoglobulin levels (IgA, IgM, and polyvalent immunoglobulin) reactive with *C. difficile* for groups of adult carriers of the *C. difficile* organism was significantly higher than the levels among patients with symptomatic infection and normal controls (34). The higher levels in the carriers might reflect the ability of the host to mount an effective immune response and prevent overt infection. During natural *C. difficile* infection, most patients develop a modest increase in toxin A or B specific serum antibodies during their illness (35–39). Despite some controversy (39), clinical recovery without relapse has been associated with a good serum antibody response to the *C. difficile* toxin (37, 38).

Local gastrointestinal IgA production may also be an important factor in the prevention of *C. difficile* infection (39, 40). A specific intestinal secretory IgA occurs primarily in the colon, the site of infection (40). This antitoxin has been postulated to protect against colitis induced by *C. difficile* by inhibiting the binding of the pathogenic toxin A to its epithelial cell receptor.

Gammaglobulin Treatment. The role of serum immunoglobulin in preventing relapse of *C. difficile* infection is exemplified by a patient I am treating at The Mount Sinai Hospital. She has had at least 12 documented relapses of *C. difficile* colitis. She responds promptly to the usual therapy, but relapses clinically and microbiologically within one month. Her *C. difficile* organism has been cultured and found to be sensitive to all antibiotics tested, including vancomycin and metronidazole. Immunologic evaluation revealed a subtle deficiency of IgG, subclass 1. Immunoelectrophoresis of her serum showed very low levels of antibodies to the *C. difficile* organism. She has been treated for more than one year with intravenously administered gammaglobulin. She has had an increase in serum *C. difficile* antibody level concurrent with a cessation of her clinical relapses.

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Lyme Disease:

Insights into the Use of Antimicrobials for Prevention and Treatment in the Context of Experience with Other Spirochetal Infections

GARY P. WORMSER, M.D.

Abstract

Unanswered questions in the management of patients with Lyme disease or those who have had *Ixodes* tick bites include: Is antimicrobial therapy effective in preventing Lyme disease during the incubation period of the infection? Which oral agents are most effective in treatment? Are macrolides efficacious? For how long a time should antimicrobial therapy be given?

Potentially useful insights into these questions can be gained by examining experience with other spirochetal infections. Using this information in conjunction with existing data from recent studies on Lyme borreliosis, tentative answers to these questions can be formulated. A short course of antibiotic therapy, perhaps even a single dose, can be anticipated to be effective in preventing Lyme disease after a tick bite. Beta-lactam drugs, such as amoxicillin, and tetracycline preparations, such as doxycycline, are the mainstays of oral therapy for treatment of active infection. Macrolides are less effective, but their utility is likely to be improved if they are given in maximal dosage. There is no convincing evidence for extending treatment of early Lyme disease beyond 14 days. There is also no evidence that longer therapy is more efficacious for other manifestations of Lyme disease, although this issue deserves further study.

IN THE UNITED STATES, forums for the discussion of management of patients with Lyme disease or of persons with *Ixodes* tick bites are sure to stimulate a lively debate (1–3). Although much of the

uncertainty surrounding optimal antimicrobial regimens is plainly due to insufficient data, perhaps equally important is the lack of agreement among practitioners as to just who has Lyme disease, a topic discussed in detail elsewhere (4, 5). Not unexpectedly, the etiologic agent of Lyme disease, *Borrelia burgdorferi*, has many biologic similarities to that of other human pathogenic spirochetes, such as *Treponema pallidum*, *Leptospira interrogans*, and relapsing fever *Borrelia* spp. For example, the generation times of these spirochetal organisms are much longer (6 to >30 hr) than those of more common human pathogens such as staphylococci or Enterobacteriaceae; and illness due to each of these spirochetal agents is characterized by a relapsing course and the potential involvement of many organs, including the central nervous system (6–12).

Antibiotics were first used in the treatment of erythema migrans by Hollstrom in the late 1940s (13), only a few years after the first report,

Adapted from the author's Grand Rounds presentation at Mount Sinai Medical Center April 20, 1994. Final revision received Nov. 1994. From the Division of Infectious Diseases, Westchester County Medical Center and New York Medical College, Valhalla, NY 10595. Address reprint requests and correspondence to Gary P. Wormser, M.D., Division of Infectious Diseases, Room 209SE, Macy Pavilion, Westchester County Medical Center, Valhalla, New York 10595.

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in 1943, of the efficacy of penicillin in patients with syphilis (14). Although current treatment guidelines for syphilis (15, 16) are not free of controversy, particularly for patients immunocompromised because of concomitant human immunodeficiency virus infection (17–21), antibiotic therapy has clearly been immensely successful in management of this illness. For example, prior to World War II, patients with general paresis comprised 5–10% of all first admissions of psychotic patients to psychiatric hospitals (22–24). Now such patients are rarely encountered in or outside of psychiatric institutions. Furthermore, treatment regimens for syphilis have been based on 50 years of clinical experience with an enormous number of patients worldwide. From 1943 to 1992, over 7 million cases of syphilis were reported to the United States Public Health Service alone (25). Over the period 1982–1992, in which approximately 50,000 cases of Lyme disease were reported in the United States, over 1 million cases of syphilis were diagnosed (25, 26).

For purposes of this discussion, management of individuals infected with *B. burgdorferi* is considered in the context of knowledge of other spirochetal diseases.

Prevention of Lyme Disease After a Tick Bite

Treatment of asymptomatic individuals who have recently had *Ixodes* tick bites will be addressed first. Three prospective placebo-controlled studies have been published, all involving volunteers from the northeastern United States (Table 1) (27–29). In each study, the antibiotic regimen employed was identical to what might be considered a “standard” treatment course for early Lyme disease associated with erythema migrans: 10 days of either amoxicillin, a penicillin

preparation, or tetracycline. Although no clinical disease developed in any of the volunteers who received an antibiotic, too few individuals were enrolled in each of the studies to conclude that antimicrobial therapy was more effective than placebo in preventing Lyme disease. In fact, even when the studies are combined by meta-analysis (Warshafsky, S. Unpublished data, 1994), there is still no significant difference in outcome between treated and untreated volunteers.

It should not be considered obvious that antibiotics are effective in this usage. Antimicrobial regimens known to be successful for therapy of active infections are not necessarily effective for treatment of incubating illness. Rickettsial diseases, for example, are highly responsive to short courses of the rickettsiostatic agents tetracycline or chloramphenicol, but are not successfully prevented, and in fact may only be postponed, by the same therapies when used before the onset of clinical illness (30, 31).

On the other hand, convincing evidence exists that a dose of benzathine penicillin G equivalent to the usual therapy of primary syphilis (2.4 million units), and even a single dose of the much shorter acting penicillin, procaine penicillin G (2.4–4.8 million units), are highly successful in preventing syphilis after sexual contact with an infected person (32). Similarly, good evidence exists that a 200-mg dose of doxycycline is highly effective in preventing leptospirosis when that agent is administered orally once weekly to individuals over the period of risk (33).

Thus, it would be anticipated that a short course of an antibiotic, perhaps even a single dose of a long-acting drug such as doxycycline (serum half-life, 18–22 hours [34]), would successfully prevent Lyme disease after a tick bite. In contrast to the approach adopted in the published trials of

TABLE 1
Efficacy in Controlled Trials of Antimicrobial Therapy in Preventing Lyme Disease after a Tick Bite

Author year (ref)	Regimen	No. of cases, Lyme disease	
		Antibiotic	Placebo (%)
Costello 1989 (27)	Phenoxymethylpenicillin 250 mg QID × 10 days	0/27	1/29 (3.4%)
Shapiro 1992 (28)	Amoxicillin 250 mg TID × 10 days	0/192	2/173 (1.2%)
Agre 1993 (29)	Penicillin* 250 mg QID × 10 days	0/89	1/90 (1.1%)
	Age <9 years		
	Tetracycline 250 mg QID × 10 days Age ≥9 years		

* Type of penicillin preparation not provided in reference.

TABLE 2
Efficacy and Duration of Therapy for Selected Antimicrobial Agents in the Treatment of Spirochetal Infections

	Agent*				Duration
	Penicillin	Tetracycline	Erythromycin	Ceftriaxone	
Syphilis	XX	X	X	X	10–14 days†
Leptospirosis	XX	X	?	?	5–7 days
Relapsing fever	X	XX	X	?	5–10 days single dose
Tick-borne Louse-borne					
Lyme disease	X	X	?	X	??

X, active; XX, treatment of choice; ?, effectiveness not known.

* Adapted from refs. 6, 7, 9, 10, 15, 16, 18, 20, 36, 39–41, 49, 54–74.

† Neurosyphilis, when treated specifically with IV penicillin.

antibiotic prophylaxis, utilization of single-dose therapy would serve to maximize compliance, while at the same time minimizing the risk of adverse drug reactions. A study comparing a single 200-mg dose of doxycycline and placebo after *Ixodes* tick bites is currently in progress in Westchester County, NY (35).

Treatment of Symptomatic Patients

Natural History of Symptoms in Untreated Patients. Although no placebo-controlled randomized treatment trials have been conducted of Lyme disease patients with erythema migrans, there are studies on the natural history of illness in untreated patients that are helpful for understanding the anticipated rate of spontaneous resolution of the erythema migrans lesion and the likelihood of extracutaneous manifestations, especially arthritis. In sum, these studies (36–38) disclose the following:

- Duration of erythema migrans ≈22 days
- Frequency of arthritis
 - by 6 months ≈30%
 - by 24 months ≈60%

Oral Antimicrobials: First-Line Therapy. Clinical experience indicates that patients with erythema migrans who receive a 10–21 day course of an oral antimicrobial, such as amoxicillin, phenoxymethyl penicillin, penicillin G, tetracycline, doxycycline, or cefuroxime axetil, resolve their acute illness more rapidly than untreated patients (36, 39–44) and are less likely to develop later objective extracutaneous manifestations of infection. The studies available, however, are of

insufficient power to exclude small to fairly substantial differences in efficacy among the individual drugs (see below).

Approximately 10%–35% of patients who have completed a course of antimicrobial therapy in recent trials have complained of intermittent subjective symptoms, such as fatigue, myalgias, or arthralgias, which usually, but not necessarily, resolve within 6 months. Unfortunately, there are still no controlled treatment trials of individuals who continue to feel unwell, including those who fulfill the criteria for fibromyalgia (45).

Further stimulus to considering such a trial is the finding by Strle et al. that *B. burgdorferi* could be recovered from normal-appearing skin at the site of a resolved erythema migrans lesion of 4 of 13 patients (31%; 95%CI, 9%–61%) from Slovenia who had received a 14-day course of doxycycline (100 mg twice daily) three months earlier (46). In contrast, Berger et al. (47) and Nadelman et al. (48) were unsuccessful in recovering *B. burgdorferi* from the site of a resolved erythema migrans lesion following therapy in 26 U.S. patients (0/26; 95%CI, 0%–11%). In the three studies, all of the patients rebiopsied were culture-positive before antibiotics were started. Further studies of posttreatment cultures may help reconcile such disparate results.

Persistence of viable treponemes has also been noted anecdotally following treatment for syphilis, particularly in the cerebrospinal fluid of patients treated for early syphilis with a single dose of benzathine penicillin (2.4 million units) (19). The rationale put forward for the survival of *T. pallidum* in such treated patients is that cerebrospinal fluid levels of penicillin after administration of the benzathine penicillin preparation are consistently below what has been considered

the "minimum" therapeutic level of .018 mcg/mL (12, 49–53).

Macrolides: Second-Line Therapy. Penicillins and tetracycline preparations, as well as the macrolide erythromycin, are regarded as effective in the treatment of early syphilis and relapsing fever. The efficacy of macrolide therapy in Lyme borreliosis (and in leptospirosis) is less clear (Table 2) (6, 7, 9, 10, 15, 16, 18, 20, 39, 40, 49, 54–74). Macrolides are unquestionably highly active against *B. burgdorferi* in vitro (75); their clinical utility in Lyme disease is open to question.

In 1983 Steere et al. (41) reported on a trial comparing erythromycin (preparation not stated) at a dose of 250 mg four times daily to a similar dose schedule of either phenoxymethyl penicillin or tetracycline. Erythema migrans and its associated symptoms resolved significantly more slowly in patients receiving erythromycin ($p < .05$). Also, a greater proportion of erythromycin-treated patients (17%) required retreatment because of persistence of symptoms or immediate relapse, although the frequency of this was not significantly different from what was observed with the other treatment modalities. Four of 29 patients (14%) receiving erythromycin developed at least 1 attack of arthritis after therapy, compared to 2/39 (5%) who received tetracycline ($p = .39$) and 3/40 (8%) ($p = .44$) who were treated with penicillin. Patients in this study were followed up for up to three years.

Evidence that even this low dose of erythromycin altered the natural history of infection is suggested by comparing the frequency of the development of arthritis in the erythromycin-treated patients to that observed among a separate group of 55 untreated patients with erythema migrans in whom arthritis developed in 62% over an approximately comparable period of follow-up (37, 38). Erythromycin therapy appears to have been approximately 70% effective (Fig.) in preventing arthritis (4/29 vs 34/55, $p < .0001$). The use of only 1 gm/d of erythromycin may have contributed to the apparent lesser effectiveness of this drug in the Steere study, since it is known that the outcome of erythromycin therapy of early syphilis is directly dependent on drug dosage (59, 67, 76).

Four published studies have compared the efficacy of azithromycin to other antimicrobials in patients with early Lyme disease (42, 46, 77, 78). Methodologic concerns, including lack of blinding, small sample size, and—for one of the studies—possible selection bias inherent in a subset analysis, limit the usefulness of the results. In all

four studies, however, azithromycin was at least as effective as the comparator (doxycycline, phenoxymethyl penicillin, or amoxicillin plus probenecid).

Luft et al. (79), in a separate randomized, double-blind multicenter study, compared azithromycin 500 mg once daily for 7 days with amoxicillin 500 mg three times daily for 20 days in 246 U.S. patients with erythema migrans. The preliminary results of this study indicate that azithromycin was significantly less effective in resolving the signs and symptoms of acute Lyme borreliosis (84/111 (76%) vs 93/106 (88%), $p < .024$) and significantly more likely to be associated with clinical relapse (17/106, or 16%, vs 4/103, or 4%; $p < .005$). It is conceivable that a longer course or a higher dose of azithromycin would have improved the outcome in the Luft study. The rate of resolution of the erythema migrans lesion per se was in fact equivalent in both treatment groups (B. Luft, unpublished data, 1994). In addition, significantly fewer azithromycin-treated patients developed arthritis after treatment than did untreated historical controls followed up for an approximately comparable time period of 6 months (37, 38 [Steere AC, personal Communication, 1994]).

The worst outcome observed for a macrolide was reported by Hansen et al. (80), who randomized a group of European patients with erythema migrans to receive either roxithromycin (a macrolide not available in the United States) 150 mg twice daily or phenoxymethyl penicillin 1 gm twice daily, each for 10 days. The study had to be interrupted prematurely when 5 (56%) of the first 9 patients treated with roxithromycin were judged to be treatment failures.

In sum, although both erythromycin and azithromycin have evidence of biological activity in Lyme disease, they should not at present be considered to be first-line therapy for this infection.

Insufficient Sample Size in Trials. The majority of treatment trials in Lyme disease have had an insufficient sample size to establish a difference in efficacy rate; just 12% was the difference observed between treatment groups for resolution of acute illness in the Luft study. In one randomized trial in which amoxicillin (plus probenecid) was compared with doxycycline, 35 evaluable patients with erythema migrans received doxycycline and 37 the amoxicillin regimen (44). Ninety-four percent (33/35) of the doxycycline-treated group had no post-treatment complaints, compared to 86% (32/37) of the amoxicil-

lin-treated group ($p = .43$). Because of the small sample size, the 95% confidence interval surrounding the 8% advantage in efficacy for doxycycline is wide, ranging from a possible 22% greater efficacy for doxycycline to a 6% greater effectiveness for the amoxicillin regimen.

Duration of Therapy

The length of time antimicrobials need to be given to patients with Lyme disease is unknown. Several lines of reasoning suggest that the duration of therapy need not be prolonged, and that a course of therapy of 2 weeks, or less, is adequate. Although most of the evidence for this conclusion concerns the treatment of early disease associated with erythema migrans, there is no compelling reason to believe that a longer treatment course is needed for other manifestations of Lyme disease.

First, experience with other spirochetal diseases suggests that 7–14 days of antimicrobial therapy is sufficient even for manifestations that may arise well over a decade following initial infection, such as neurosyphilis (Table 2) (6, 7, 15, 16, 49, 61, 63, 68). Epidemic louse-borne relapsing fever, which has been associated with a mortality rate of up to 40% in untreated patients (7, 9), is in fact reliably treated by a single 500 mg dose of either tetracycline or erythromycin.

Second, in the studies of Johnson and coworkers (81) and Mursic and coworkers (82) using animal systems of *B. burgdorferi* infection, 5–7 days of the most active antimicrobials tested, given in an appropriate dose for the model, was curative based on the absence of detection of the spirochete by organ cultures done at the time the animals were killed. These studies did not evaluate whether an even shorter course of therapy might have proved equally effective.

Third, Weber et al. (83) conducted a prospective randomized multicenter trial comparing a 5-day course of ceftriaxone (1 gm intramuscularly daily) with a 12-day course of phenoxymethyl penicillin (1 million units orally 3 times daily) in 73 European patients with erythema migrans. There was no significant difference between therapies in the generally favorable outcome observed. Thirty-four of 40 ceftriaxone-treated patients (85%) and 25 of 33 who received penicillin (76%) ($p = .38$) were free of symptoms over the mean follow-up period of 10 months.

It could be argued that the 5-day course of ceftriaxone was successful largely because of the much higher blood levels associated with parenteral therapy. This reasoning, however, is incon-

Erythromycin Trial

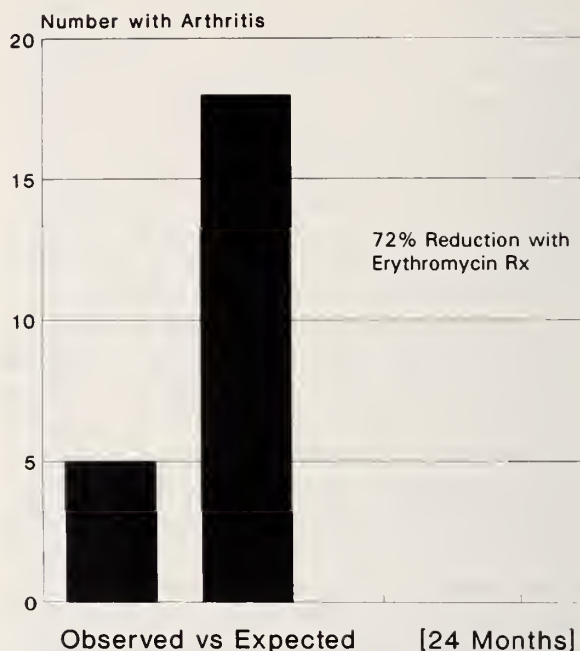


Fig. Incidence of arthritis over approximately 24 months in patients with erythema migrans treated with erythromycin (41), compared to other patients with erythema migrans who did not receive antibiotic therapy (37).

sistent with the observed pharmacodynamics of ceftriaxone, as reported by Luft et al. (57), who showed that the rate of killing of *B. burgdorferi* in vitro was not accelerated by increasing the concentration of ceftriaxone. (The pharmacodynamics of penicillin for rabbits with *T. pallidum* orchitis differ in that the rate of treponemicidal action of penicillin increases progressively over a fiftyfold range of serum concentrations [50].) Whether the excellent central nervous system penetration of ceftriaxone actually translates into clinical outcomes for patients treated with this agent superior to outcomes among those who receive a considerably longer course of an oral antimicrobial is worthy of further investigation.

Conclusions

Beta-lactam antimicrobials, such as penicillin, amoxicillin, and certain third-generation cephalosporins (for example, ceftriaxone), as well as tetracyclines (for example, doxycycline), are highly effective treatment modalities for Lyme disease and other spirochetal infections. A short course of antimicrobial therapy (perhaps one dose of doxycycline) may well be effective in preventing Lyme disease after tick bites; a prospective study addressing this question is currently in progress.

Macrolides are also active against spirochetes, including *B. burgdorferi*. The clinical efficacy of these agents in Lyme disease, however, has been less than that of comparators in certain studies. For this reason, macrolides should be considered second-line therapy. If Lyme disease proves to be similar to syphilis in treatment response, higher doses of macrolides may be anticipated to provide better clinical results.

There is as yet no convincing evidence that a course of antimicrobial therapy longer than 14 days improves clinical outcome for patients with any manifestation of Lyme disease. However, more studies on this topic are needed.

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Advances in Lung Cancer?

As a youngster, I believed that old people were expected to contract cancer—it was the order of things. Years later, Irving J. Selikoff quoted Richard Doll to the effect that lung cancer is not inevitable with age—that it is almost always environmentally induced. Irving Selikoff's own commanding work showing smoking and asbestos to be carcinogens (1, 2) handed us what is unfortunately our current most efficacious approach to the problem of non-small-cell lung cancer: prevention (3).

That prevention rather than treatment is still our most reliable resort is clear from my own review of the outcome of non-small-cell lung cancer in 200 patients treated for it in my outpatient office, 100 of them consecutively treated from 1978 to 1980, the other 100 consecutively treated from 1989 to 1990. Of the first group, 28 were considered to be "completely resected" by their surgeons at the time of thoracotomy. Today, only 8 of those patients either cannot be found or are alive—a cure rate of, at best, 8%. Of the second group of 100, 38 were identified by their surgeons as "completely resected" at the time of operation. Yet less than two years later, 20/38 had recurrence of cancer. I have no doubt that in the year 2000 the outcome for this second group of 100 patients will also be a cure rate of about 8%.

I think those results reasonably represent the immobility in our knowledge of lung cancer from 1980 to 1990 and the true state of lung cancer prognosis today. The advent of CT scanning and our ability to better detect mediastinal and occasionally pleural metastases preoperatively, and thus to exclude from surgery and its burdens patients who have obvious intrathoracic metastases, probably account for the higher number of patients initially identified by their surgeons as "completely resected" in the group treated in 1989–1990. Yet we still await a less dismal future for patients with non-small-cell cancer.

At a Grand Rounds held at the Mount Sinai Medical Center on November 26, 1993 that I moderated, "Advances in Lung Cancer?" two presentations reviewed what we know now. Those two discussions have been adapted for publication here. Steven Keller surveys for us the current status of surgical treatment—still, as he reminds us, the only potentially curative therapy, despite advances in radiation and medical oncology. Stuart Aaronson reviews the potential new paths opened up by molecular biology, certainly a quarter offering us hope for improvement in our ability to treat the public health scourge of lung cancer.

—Alvin Teirstein, M.D.

*Rosenfield and Solomon Professor of Medicine
Director, Division of Pulmonary and Critical Care Medicine
Department of Medicine
The Mount Sinai Medical Center*

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Surgical Treatment of Non-Small-Cell Lung Cancer

STEVEN M. KELLER, M.D.

LUNG CANCER is currently the most common cause of cancer deaths in both men and women (1). During the past decade numerous studies documenting the efficacy of surgery, radiotherapy, and chemotherapy administered individually or in combination have been published. I review those clinical trials and reports germane to the surgical treatment of non-small-cell lung cancer (NSCLC).

In an attempt to decrease the incidence of this public health scourge, the National Cancer Institute has proposed a reduction of the amount of tar contained in each cigarette and a diminution in the prevalence of smoking to 15%. Analysts have projected that the implementation of these proposals by the coming millennial year 2000 will result in a decrease in the numbers of male and female deaths from lung cancer in the year 2025 to 50% and 90%, respectively, of those that occurred in the year 1980 (2). Surgery remains the only potentially curative treatment, despite advances in radiation and medical oncology.

Staging

The system of staging by classifying the primary tumor (T), the regional nodes (N), and metastasis (M) was modified in 1986 by the American Joint Committee on Cancer and the Union Internationale Contre Cancer (UICC) in order to

allow the staging categories to better reflect current treatment approaches. The adopted changes were designed to create groups that had similar therapies and survival rates. The most significant alterations included creation of the T4 and N3 categories, as well as stages IIIa, IIIb, and IV (Tables 1-2).

The modified staging system has been shown to reliably predict outcomes in both prospective and retrospective studies (4, 5). However, not all of the stages are truly homogeneous with regard to either treatment or prognosis. Though survival following resection of pathologic stage I NSCLC is generally reported to be in the range of 70%, the reported survival of patients with T1 tumors is consistently better than those patients with T2 neoplasms. Similarly, stage IIIa includes both patients with N2 lymph node involvement and those with chest wall extension (T3) but no lymph node metastases. Patient survival with the latter is significantly different from that of patients with mediastinal lymph node disease. Clearly, the most accurate manner in which to report results is by the TNM categories themselves, rather than overall stage.

Preoperative staging should begin with a complete history and physical examination. The PA and lateral chest x-rays are a source of information regarding not only tumor location, but also appropriate avenues of therapy. Previous x-rays should be sought for comparison. A chest CT is performed in order to identify lymphatic or parenchymal metastases. Asymptomatic adrenal metastases may occur in 10% of patients with otherwise resectable disease. Measurement of serum chemical components is sometimes helpful in identifying hepatic and osseous metastases. The preoperative measurement of tumor-associated antigens in serum is unnecessary. Performance of routine bone scans and brain CTs or MRIs re-

Adapted from the author's Grand Rounds presentation at the Mount Sinai Medical Center on November 26, 1993. Final manuscript received July 12, 1994. From the Mount Sinai School of Medicine and the Division of General Thoracic Surgery, The Mount Sinai Hospital, New York. Address reprint requests to Steven M. Keller M.D., Chief, Division of General Thoracic Surgery, Dazian, Beth Israel Medical Center, First Ave. at 16th St, New York, NY 10003.

TABLE 1

Definitions of Primary Tumor (T) and Node (N) Categories

TX	Tumor proven by the presence of malignant cells in bronchopulmonary secretions but not visualized roentgenographically or bronchoscopically, or any tumor that cannot be assessed as in a retreatment staging.
T0	No evidence given of primary tumor.
TIS	Carcinoma in situ
T1	A tumor 3.0 cm or less in greatest dimension, surrounded by lung or visceral pleura, and without evidence of invasion proximal to a lobar bronchus at bronchoscopy
T2	A tumor more than 3.0 cm in greatest dimension, or a tumor of any size that either invades the visceral pleura or has associated atelectasis or obstructive pneumonitis extending to the hilar region. At bronchoscopy, the proximal extent of demonstrable tumor must be within a lobar bronchus or at least 2.0 cm distal to the carina. Any associated atelectasis or obstructive pneumonitis must involve less than an entire lung.
T3	A tumor of any size with direct extension into the chest wall (including superior sulcus tumors), diaphragm, or the mediastinal pleura or pericardium without involving the heart, great vessels, trachea, esophagus or vertebral body, or tumor in main bronchus within 2 cm of carina without involving the carina.
T4	A tumor of any size with invasion of mediastinum or involving heart, great vessels, trachea, esophagus, vertebral body or carina or presence of malignant pleural effusion.
N0	No demonstrable metastasis to regional lymph nodes.
N1	Metastasis to lymph nodes in peribronchial or ipsilateral hilar region, or both, including direct extension.
N2	Metastasis to ipsilateral mediastinal lymph nodes and subcarinal lymph nodes.
N3	Metastasis to contralateral mediastinal lymph nodes, contralateral hilar lymph nodes, ipsilateral or contralateral scalene or supraclavicular lymph nodes.

mains controversial, although in the absence of symptoms the yield is certainly low (6, 7).

Patients with a new lung mass suggestive of NSCLC may undergo surgery without a histologic diagnosis. A nondiagnostic bronchoscopic or percutaneous needle biopsy would not change the therapeutic recommendation and is, therefore, unnecessary. Patients with the rare small-cell lung cancer that appears as a solitary nodule benefit from surgery, and this uncommon scenario should not be utilized as justification for routine preoperative biopsies (8). However, if the treatment goal is palliation rather than cure, bronchoscopy or percutaneous needle biopsy is necessary to establish a diagnosis. Approximately half of patients with NSCLC will be found to have

TABLE 2

Stage Grouping of Subsets by Tumor (T), Node (N), and Metastasis (M) Categories

Stage	T	N	M
Occult CA	TX	N0	M0
Stage 0	TIS	Carcinoma	in situ
Stage I	T1	N0	M0
	T2	N0	M0
Stage II	T1	N1	M0
	T2	N1	M0
Stage IIIa	T3	N0	M0
	T3	N1	M0
	T1-3	N2	M0
Stage IIb	Any T	N3	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

stage IV disease. Inoperable locally advanced disease (stages IIIa and IIb) is found in another 10% of patients. Only 40% of patients have disease amenable to surgical resection (stages I, II, IIIa) (9).

Intraoperative staging is crucial for the accurate reporting of results, and proper staging performance is the responsibility of the surgeon. Visual inspection or digital palpation of lymph nodes is unreliable. Either a complete mediastinal lymph node dissection or nodal sampling must be performed. The American Thoracic Society has described the mediastinal lymph node levels by their relation to constant anatomic structures (10). A complete mediastinal lymph node dissection lengthens the operation by only a brief

TABLE 3

Survival following Resection of Non-Small-Cell Lung Cancer

Author (ref)	N	5 yr Survival (%)
Stage I		
Martini (32)	115	77*
Pairolero (33)	328	65
Williams (34)	331	72
LCSG (35)	907	65†
Stage II		
Martini (36)	75	50‡
Newman (37)	20	40
Ferguson (38)	34	30
Martini (39)	214	39
Chest Wall (T3N0)		
Piehlner (40)	31	54
Trastek (41)	29	38
McCaughan (42)	66	56
Albertucci (43)	21	41

* 3 yr survival.

† T1N0 only; approximate.

‡ Some patients received adjuvant therapy.

interval and is associated with little morbidity (11).

Preoperative Evaluation

Both the cardiac and pulmonary systems require particular scrutiny prior to thoracic surgery. Patients with no history of cardiac disease and who have normal findings on physical examination and EKG require no further cardiac evaluation. Similarly, patients with stable, well-controlled cardiac disease can undergo resection with little increase in risk. Previously unrecognized, unstable, or poorly controlled cardiac disease requires further evaluation and treatment prior to surgery. Atrial arrhythmias may occur in as many as 20% of patients and are more common following pneumonectomy (12). The efficacy of digitalis prophylaxis remains unproven (13).

Each patient should undergo pulmonary function testing and arterial blood gas assessment. Increased morbidity is associated with arterial pO_2 under 60 mm Hg or pCO_2 over 45 mm Hg. DLCO under 60% of predicted and MVV of 35% are predictive of postoperative complications. The FEV₁ is perhaps the best single test. Postoperative FEV₁ over 800 cc, and preferably over 1 L, is necessary to avoid respiratory failure. A split-function ventilation perfusion scan should be obtained if the preoperative FEV₁ is under 2 L in order to document how much function is contributed by the affected lung. When complete resection requires an unplanned pneumonectomy, this information may be crucial.

Indwelling bladder and arterial catheters as well as a pulse oximeter are routinely employed during surgery. Collapse of the ipsilateral lung and selective ventilation of the contralateral lung are achieved with a double-lumen endotracheal tube. Perioperatively, antibiotics are administered to all patients, and lower extremity compression boots are employed as prophylaxis for deep vein thrombosis.

Operative Procedure

Lobectomy replaced pneumonectomy as the procedure of choice for all stages of NSCLC in the late 1950s, though equal efficacy was never demonstrated in a randomized trial. A prospective randomized trial conducted by the lung cancer study group (LCSG) has refuted the claim of some surgeons that wedge resection or formal segmentectomy for stage I NSCLC produces results similar to lobectomy (14). A threefold increase in local recurrence results when a "more conservative" operation is performed. When the patient's

pulmonary function permits, lobectomy is the procedure of choice. Video thoracoscopy may be utilized provided it does not compromise patient treatment.

Following a successful operation, the patient must be regularly evaluated for evidence of cancer recurrence. A careful history and physical examination, along with a chest x-ray, are sufficient to identify the majority of metastases or local recurrences. Routine measurement of serum chemical levels and tumor-associated antigens and chest CTs are not indicated.

Narcotic analgesia is rarely required for longer than eight weeks. A post-thoracotomy pain syndrome characterized by pain along the incision, in the mid-back and beneath the breast will develop in approximately 10% of patients (15). Nonsteroidal anti-inflammatory agents and a tricyclic antidepressant are frequently successful in ameliorating this difficult problem.

The cardiopulmonary systems are the sites of the majority of complications following pulmonary resection. Clinically significant pneumonia occurs in less than 3% of patients, although asymptomatic atelectasis occurs commonly (16). Wound infections are essentially nonexistent and bronchopleural fistulas occur only rarely. Approximately 20% of patients require blood transfusion (17). Mortality following pneumonectomy and lobectomy approximate 7% and 3%, respectively (18).

Adjuvant and Neoadjuvant Therapy

Following complete resection of pathologic stage I NSCLC, survival ranges between 60% and 80% (Table 3). Although the practical evaluation of additional treatment is difficult because of the excellent results following surgery, the potential role of adjuvant therapy has been addressed. A randomized prospective trial comparing postoperative intrapleural administration of Bacille Calmette-Guerin (BCG) to placebo was conducted by the LCSG. No survival advantage was found (19). The LCSG later compared CAP chemotherapy

TABLE 4
Subgroups of N2 Disease

	Mediastinum chest x-ray	Chest CT	Mediastinoscopy	Thoracotomy
1	Normal	NA	NA	+
2	Widened	NA	NA	+
3	NA	NA	—	+
4	NA	NA	+	+
5	NA	+	NA	+

(cyclophosphamide 400 mg/m², doxorubicin 40 mg/m², cisplatin 40 mg/m²) to an untreated control arm, and again no survival advantage was found for those patients who had received chemotherapy (20).

In contradistinction, a recently completed phase III trial comparing six cycles of monthly CAP (cyclophosphamide 400 mg/m², doxorubicin 40 mg/m², cisplatin 40 mg/m²) to controls who received no treatment demonstrated a significant increase in disease-free survival (21). However, before the routine administration of adjuvant chemotherapy for patients with resected stage I NSCLC can be recommended, independent confirmation is required.

Patients who have undergone resection of stage I NSCLC develop second primary tumors at a rate of 1% per year (22). The cancer cooperative groups are currently conducting a phase III chemoprevention trial (Intergroup 0125) in an effort to determine whether oral 13-cis retinoic acid 30 mg daily might prevent formation of a second cancer. A four-year follow-up of the 1260 patients necessary for this study will be required to prove or disprove the utility of this drug.

Approximately 10% of patients with NSCLC are pathologically stage II, T1N1 or T2N1. Because the difference between stage II and stage IIIa may depend on the zeal with which the surgeon pursues a lymph node dissection, survival statistics vary widely. The Memorial Sloan-Kettering Cancer Center has reported a median survival of 54 months, although other smaller retrospective series have published median survivals of 12–14 months (Table 3). The presence of metastatic tumor within a single nodal level is associated with the longest survival.

The LCSG has reported three phase III trials that included patients with stage II NSCLC. CAP chemotherapy (cyclophosphamide 400 mg/m², doxorubicin 40 mg/m², cisplatin 40 mg/m²) administered in six one-month cycles was compared to a control arm of patients receiving intrapleural BCG. No advantage for immunotherapy was noted (23). In another study, patients received either RT (5000 cGy, 180–200 cGy/daily fx) or no further treatment following complete resection of all stage II disease. No survival advantage was noted, although there was a decrease in local recurrence (24). A small number of patients with pathologic stage II disease were included in a trial comparing the combination of RT (4000 cGy in 2000 cGy split course fractions) and CAP (cyclophosphamide 400 mg/m², doxorubicin 40 mg/m², cisplatin 40 mg/m²) to RT alone. The patients

who received the combination therapy had a median time to recurrence of 14 months, significantly greater than the six months for those patients treated with RT alone. However, conclusions regarding therapeutic recommendations could not be reached because of the relatively few patients with stage II disease (25).

Intergroup Trial 0115, a prospective randomized trial comparing concomitant RT (5040 cGy in 180 cGy daily fx) and chemotherapy (cisplatin 60 mg/m² and etoposide 120 mg/m²) to RT alone, has been designed to test the utility of adjuvant therapy. Measurements of the ability of chemotherapy and radiotherapy to prolong survival and prevent local recurrence are the objectives of this study. Patients with resected stage II NSCLC should be carefully observed or offered participation in an approved investigation.

The treatment and prognosis of the two major subcategories of stage IIIa, T3N0 and T1-3N2, differ so substantially that they are best considered separately. Patients with peripheral chest wall invasion (T3) should undergo resection of the involved ribs and underlying lung. Five-year survival rates approximate 50% (Table 3). Marlex mesh and methyl methacrylate are utilized to repair large defects that are not covered by the chest wall musculature. The preoperative demonstration of mediastinal lymph node metastases is considered a contraindication to surgery.

The most controversial issues in the treatment of patients with NSCLC relate to suspected or documented N2 disease. As a result of the variety of methods in which investigators have reported their results, comparative analysis of the literature is not possible. There exist five unintentionally created subgroups of N2 disease that were defined by whether the presence or absence of N2 disease was assumed because of a chest x-ray or CT scan or whether mediastinoscopy was routinely performed (Table 4).

Surgeons at Memorial Sloan-Kettering Cancer Center reported 30% five-year survival for 151 completely resected patients with clinical N0 or N1 disease (subgroup 1) (26). They maintained that prethoracotomy mediastinoscopy was unnecessary, since in their hands more than 90% of the patients were resectable. However, the tumors of those patients whose chest x-rays demonstrated bulky mediastinal disease (subgroup 2) were rarely resectable. Furthermore, survival was dismal in those few patients whose tumors were completely removed. The researchers concluded that patients with bulky mediastinal lymph nodes should have the metastatic disease histo-

logically documented and then be either treated in a palliative fashion or offered participation in a neoadjuvant protocol.

Five-year survival of 40% in patients found to have N2 disease following a (falsely) negative mediastinoscopy (subgroup 3) has been well documented (27). Survival following resection of N2 disease previously demonstrated at mediastinoscopy was associated with only 15% 5-year survival (subgroup 4). A similar percentage, 20% five-year survival, was found in patients with presumed N2 disease identified on preoperative CT scan and later confirmed during a complete resection (28). Patients who survive five years generally have tumor limited to a single mediastinal nodal level.

Patients are eligible for participation in Intergroup Adjuvant Therapy Trial 0115 if they are found to have N2 disease following complete resection. Those who refuse participation should be closely observed or treated with mediastinal radiotherapy. The latter has no impact on survival, although it is effective in preventing local recurrence (24).

Three treatment options may be offered to patients in whom bulky or multi-mediastinal-nodal level N2 disease is histologically documented prior to surgery: observation, palliative radiotherapy, or participation in an approved neoadjuvant therapy protocol. The ability of platinum-containing regimens to convert inoperable disease into technically resectable tumor has been demonstrated in numerous phase II trials (29, 30). Five-year survival as high as 26% has been documented. Since no randomized trial has yet proven efficacy, patients should be treated only within approved protocols. An intergroup neoadjuvant trial has recently been activated. The presence of metastases in N3 lymph nodes or invasion of mediastinal structures (stage IIb) is generally considered a contraindication to surgery. However, a projected 40% two-year survival was seen in a group of patients treated in a phase II Southwest Oncology Group trial (31).

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Lung Cancer:

Emerging Therapeutic Approaches based on Molecular Genetics

STUART AARONSON, M.D.

I BRIEFLY SUMMARIZE here some of the knowledge gained in recent years about the molecular changes that lead to cancer, particularly lung cancer. Then I try to provide general insights into how we may be able to use this knowledge to develop better approaches to intervention in this disease and other types of cancers as well.

Molecular Changes Leading to Cancer

The general scheme by which a progenitor cell becomes a fully differentiated cell involves signalling by a variety of growth factors and cytokines that cause the normal cell to proliferate and differentiate. What has become clear in almost every cancer studied is that changes in this orchestration through genetic aberrations affecting a specific set of genes that we call oncogenes activate signalling pathways that lead to uncontrolled growth. In concert with genetic events that inactivate so-called tumor suppressor genes and impair their critical growth regulatory effects, these stepwise alterations create the cancer cell.

We are now aware that both oncogenes and tumor suppressor genes appear to impinge importantly on cell-cycle control, supplanting or replacing growth factors that normally cause cells to move from the resting G0 phase through G1 and finally through mitosis. The functions of exoge-

nous growth factors such as epidermal growth factor (EGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF) can be replaced by genetic changes that upregulate growth factor expression in a manner which self-stimulates the cell by a so-called autocrine mechanism. Genetic changes can also cause constitutive growth factor receptor function, the activation of genes such as *ras* or of certain critical transcription factors, which are downstream targets of growth factor signalling. Each of these changes has been frequently observed in tumor cells. Such genes can be upregulated through mutations in their coding sequences, gene amplification, or other mechanisms causing overexpression.

Cytokines such as TGF β normally act to inhibit cell proliferation and can even do so at relatively late stages in cell cycle progression. Such cytokines also act through specific signalling pathways. The evidence is still emerging, but some of these inhibitory cytokines probably interact with tumor suppressor genes, whose loss of function may prevent such cytokines from performing their growth inhibitory functions.

In the last two or three years, investigations of one critical tumor suppressor gene, p53, have led to the understanding that another kind of checkpoint within cells is one that related to cell cycle inhibition in response to particular stresses, such as DNA damage. DNA damage induces activation of genes like p53, which under normal conditions causes the cell to arrest growth in order to repair DNA damage. The loss of p53 function in a cell that is progressing along the pathway to malignancy removes this particular kind of regulatory control. In one sense this makes the cell more sensitive to the killing effects of radiotherapy or chemotherapy. However, the adverse

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effect is that, if such a cell survives, it more rapidly accumulates additional genetic damage. This markedly increases the probability of oncogene activation and a further contribution to tumor progression.

We have learned much over the last several years about the signalling pathways triggered by growth factors and their activated receptors. Recently, two important effectors that can be activated as oncogenes, *ras* and *raf*, have been shown to undergo direct physical interaction. The *ras* gene product is a small GTP-binding protein, and the *raf* protein is a serine kinase. The *raf* kinase phosphorylates other serine kinases, leading to activation of MAP kinase. This latter enzyme causes phosphorylation of specific transcription factors that turn on the cellular machinery involved in cell proliferation.

Changes Specific to Lung Cancer

All the changes I have described can occur in a lung cancer cell. For example, genes for growth factor receptors, including the EGF receptor and *erb B-2*, are amplified and overexpressed in a reasonable fraction of lung cancers. The *ras* genes are often activated by point mutations at specific hot spots that cause their products to be constitutively turned on. P53 genes are inactivated in more than 50% of lung cancers. The retinoblastoma (Rb) tumor suppressor gene is commonly inactivated in lung carcinoma as well. If one looks at this process from one perspective, several genetic changes must occur for a lung carcinoma to emerge. For example, in mice in which p53 or Rb function has been inactivated by a targeted gene knockout, several types of tumors occur at much higher frequency than lung cancer. This probably tells us that even though p53 inactivation can occur in lung cancer, multiple changes have to take place for this malignancy to become clinically evident. In contrast, some target cells likely require fewer genetic changes to manifest a malignancy. In humans, environmental influences on lung cancer, such as smoking, undoubtedly increase the frequency of mutations and, thus, the likelihood of the multiple genetic changes required to cause this malignancy.

Emerging Therapeutic Approaches

If autocrine growth factors can be implicated in the genetic changes catalogued in lung cancers, one might envision the idea of using antagonists to ligand function to impair proliferation of the tumor cell. In lung carcinomas in which overex-

pressed receptors are present, it seems reasonable to consider the possibility of targeting radioisotopes, toxins, or prodrugs to the tumor, using either a modified ligand or monoclonal antibody directed against the receptor. As we begin to understand intracellular mitogenic signalling pathways, it may be possible to utilize such knowledge to develop other approaches to intercept aberrant signalling. One possible target might be at the level of receptor interaction with substrates whose tyrosine phosphorylation is important in mitogenic signalling. Another possible target might be the *ras* p21 molecule, which must be lipidated in order to achieve a cell membrane location required for function.

If one transfects a tumor cell which has lost p53 function with normal p53 and expresses a high level of normal p53, it is possible to significantly impair proliferation of the tumor cell in culture, and in some cases to induce programmed cell death or apoptosis. Thus, drugs which imitate the function of the normal p53 molecule might be able to specifically impair the growth of tumor cells that have lost p53 function. Finally, will it be possible to target tumors by means of gene therapy to replace the tumor-suppressor gene itself? This is likely to be feasible only if highly efficient delivery systems can be developed to cause gene replacement in a stable manner in a high proportion of tumor cells.

Over the last several years we have accumulated tremendous knowledge about the genetic changes responsible for malignant conversion. Nonetheless, we recognize that these changes occur in genes that are also critical to normal cell proliferation and differentiation. Thus, as we try to develop new rational approaches, we must address the same questions of efficacy versus toxicity as are pertinent to conventional treatment modalities. The development of innovative therapeutic approaches that translate knowledge about the molecular genetics of cancer to the clinic will be important challenges to cancer biologists over the next several years.

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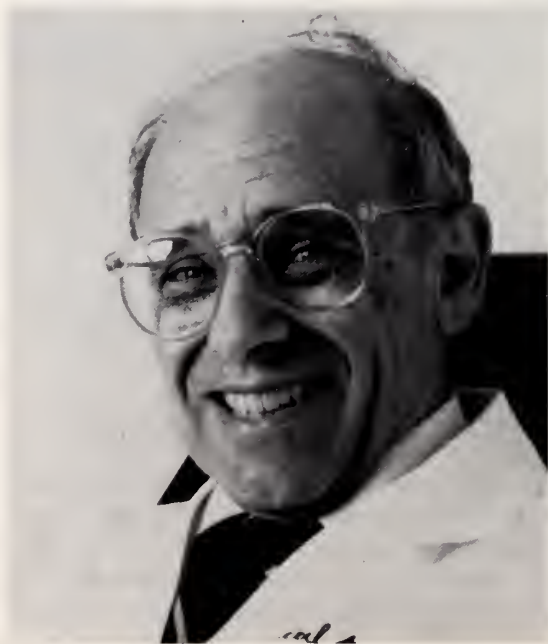
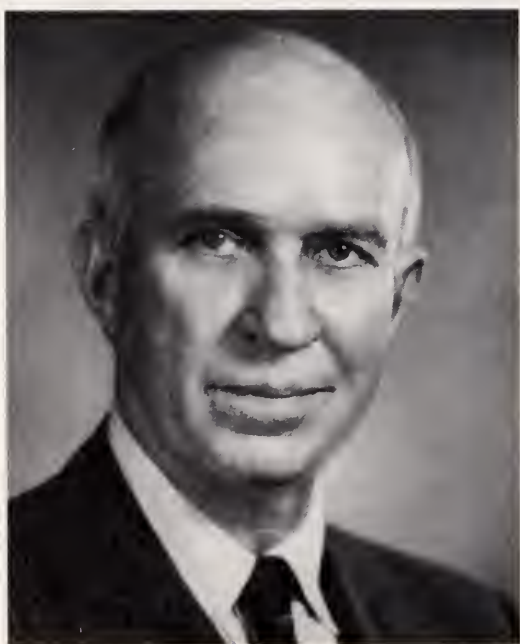


Fig. 1. Top Louis R. Wasserman. Left John H. Lawrence circa 1960-1970. Right Nathaniel I. Berlin.

Louis R. Wasserman and the History of Polycythemia Vera

NATHANIEL I. BERLIN, M.D.

WHAT I WOULD like to do is recount the development of our knowledge of polycythemia vera, because it is the research on polycythemia vera that Louis Wasserman began at the Donner Laboratory of the University of California and continued at Mount Sinai Medical Center, and his leadership in the creation of the Polycythemia Vera Study Group, that form the cornerstone of his contributions to medicine. I should not omit his contributions to the American Society of Hematology as its president, and his seminal role in creating the education program of the society's annual meeting.

In 1892, Vaquez, a French physician, described a single case of the disorder in the *Comptes Rendus des Seances de la Societe de Biologie et ses Filiales* (1). More than a decade later, in 1903, Osler wrote a frequently cited paper, "Chronic cyanosis with polycythemia and enlarged spleen," published in the *American Journal of Medical Sciences* (2), at that time a major medical journal. Osler's interesting paper describes two cases of his own, a third he learned about from a colleague, and a fourth he observed as a visitor at the Lakeside Hospital in Cleveland—just one instance of the importance in communal scientific communication of the visiting professor. Two of the four patients described in Osler's paper were Jewish. Osler also includes summaries of five cases from the literature: Vaquez's original case, three from the *Boston Medical and Surgical Journal* (predecessor of the *New England Journal of Medicine*), and one from *The Lancet*.

Osler begins thus:

The group of cases here reported, with those collected from the literature, are worthy of further study as we have here, in all probability, "a definite clinical entity and one which is new to medical science," to use the words of Saundby and Russell in describing their case. The condition is characterized by chronic cyanosis, polycythemia, and moderate enlargement of the spleen. The chief symptoms have been weakness, prostration, constipation, headache, and vertigo.

Osler divides the polycythemias into two groups: relative polycythemia and true polycythemia. He includes in the true polycythemia group both the new entity now known as polycythemia vera and the secondary polycythemias, a classification still in large measure in use.

In 1904, Parkes-Weber and Watson presented a case report at the Clinical Society of London published in the *British Medical Journal* as "Chronic polycythemia with enlarged spleen, probably a disease of the bone marrow" (3). That same year Türk, an Austrian physician, called attention to the elevated white count in the disorder (4). In 1908 Naegeli, a German physician, in his textbook *Blutkrankheiten und Blutdiagnostik*, acknowledges Vaquez's contribution in the eponymic designation "Vaquez's disease" and provides a good description of the clinical features of the disorder (5). Thus, by 1908 polycythemia vera had been recognized by French, American, British, Austrian, and German physicians.

In 1917 Ludin introduced radiation therapy to the bones (6) and in 1918 Eppinger and Kloss began treating the condition with phenylhydrazine (7). I cannot find an early description of the use of phlebotomy, although the ninth edition (1920) of Osler's textbook does mention it glancingly (8).

In 1937, Roy R. Kracke of Emory University described polycythemia vera as a "progressive and ultimately fatal disease of unknown etiology

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which is characterized by excessive numbers of red blood cells, marked splenomegaly, increased blood volume, and the symptoms resulting from these altered states," and says that "modern treatment resolves itself between a choice of two methods, that is, the use of phenylhydrazine or radiation, or both." He also notes that "the use of repeated bleedings has been practically abandoned." (Phenylhydrazine does effectively destroy red cells in the circulating blood [9].)

Kracke's description well summarizes the state of knowledge at that time. At the same time, Ernest Lawrence was just beginning what we would now call the marketing of radioactive isotopes in biomedical research. In 1939, John Lawrence (Fig. 1), Ernest's younger brother, began treating patients with radioactive phosphorus, which he first reported on in 1940 (10). He described the results in two patients (Fig. 2); each had a good hematologic response, although the interval between treatments was short and the doses used were large by the criteria in use when I joined the Donner Laboratory in 1947. During World War II, patients continued to be treated at the Donner Laboratory, but the laboratory itself specialized in aviation medicine, and I can find no additional contributions to knowledge of polycythemia vera from that laboratory until after the war.

Louis Wasserman. At this postwar point, Louis Wasserman enters the picture. In 1946 he went to study at the Donner Laboratory and began his lifelong friendship with John Lawrence. His first contribution, published in 1947, was to measure the arterial blood oxygen saturation in polycythemics (11). This work established that the arterial blood oxygen saturation in polycythemia vera is normal and became a critical diagnostic element. Wasserman then returned to The Mount Sinai Hospital but spent the summer of 1947 in Berkeley.

In June 1947 I went to Berkeley as a graduate student of Lawrence's. At my initial meeting with Lawrence, he instructed me to go to the rear of the third floor. Melvin Calvin, who later won the Nobel Prize for his work on photosynthesis, had the front part of the floor. I was to find Lou Wasserman, who would tell me what to do. Thus began my friendship with Lou.

Lou wanted to pursue two lines of study: iron metabolism, which he assigned to Rex Huff, who developed the field of ferrokinetics (12); and the polycythemia produced by cobalt. This was my assignment, and with it began my lifelong professional association with Louis Wasserman.

Establishing a Measure of Total Red Cell Volume. I completed my work as a graduate stu-

dent with a thesis entitled "Studies on the mechanism and development of the cobalt polycythemia in the rat with the aid of radioactive isotopes" (13). I did not find the mechanism by which cobalt produced polycythemia; some years later, cobalt was found to increase erythropoietin production (14). However, an important consequence of my thesis study was the introduction into the Donner Laboratory of Hevesy's method of labeling red cells with P32 to measure blood volume (15). We demonstrated (16) that rat red blood cells labeled with both P32 and Fe59 gave identical results and thus established, at least in the rat, the validity of the P32-labeled red blood cell method of measuring blood volume. John Lawrence then asked me to establish the P32-labeled red blood cell method in his patients, particularly in those who were polycythemic. Our paper (Lawrence, Gartland, and I) on the blood volume in the polycythemics was published in 1950, in the *American Journal of Medicine*, edited at that time by Alexander Gutman. He was chairman of the Department of Medicine at Mount Sinai (17).

From my perspective, these studies had two important results:

- establishing the measurement of total red cell volume by labeled red cells as an important factor in the diagnosis and management of polycythemia
- recognition of a new entity that may be the most common cause of elevated hematocrit, relative polycythemia, a persistent disorder not due to the various causes of transient relative polycythemia as described by Osler

It was John Lawrence who suggested that we call this entity "stress polycythemia," and we used this term in the title of our paper (18); a number of other names have been coined for this entity.

A significant event was the report by Byron Hall of the Mayo Clinic, at a 1948 meeting at the University of Wisconsin, of four cases of acute leukemia in P32-treated patients (19). In 1948, to the best of my knowledge, no P32-treated polycythemics at Berkeley had developed acute leukemia. Hall's report led to much discussion and considerable debate in the hematologic community and was certainly significant in leading to the formation of the Polycythemia Vera Study Group.

Ferrokinetics. At Berkeley, Rex Huff opened up the field of ferrokinetics (Fig. 3). He conceptualized a model of iron metabolism in which the flow of iron in the plasma was central. Basically, Huff reasoned that if he could measure the turn-

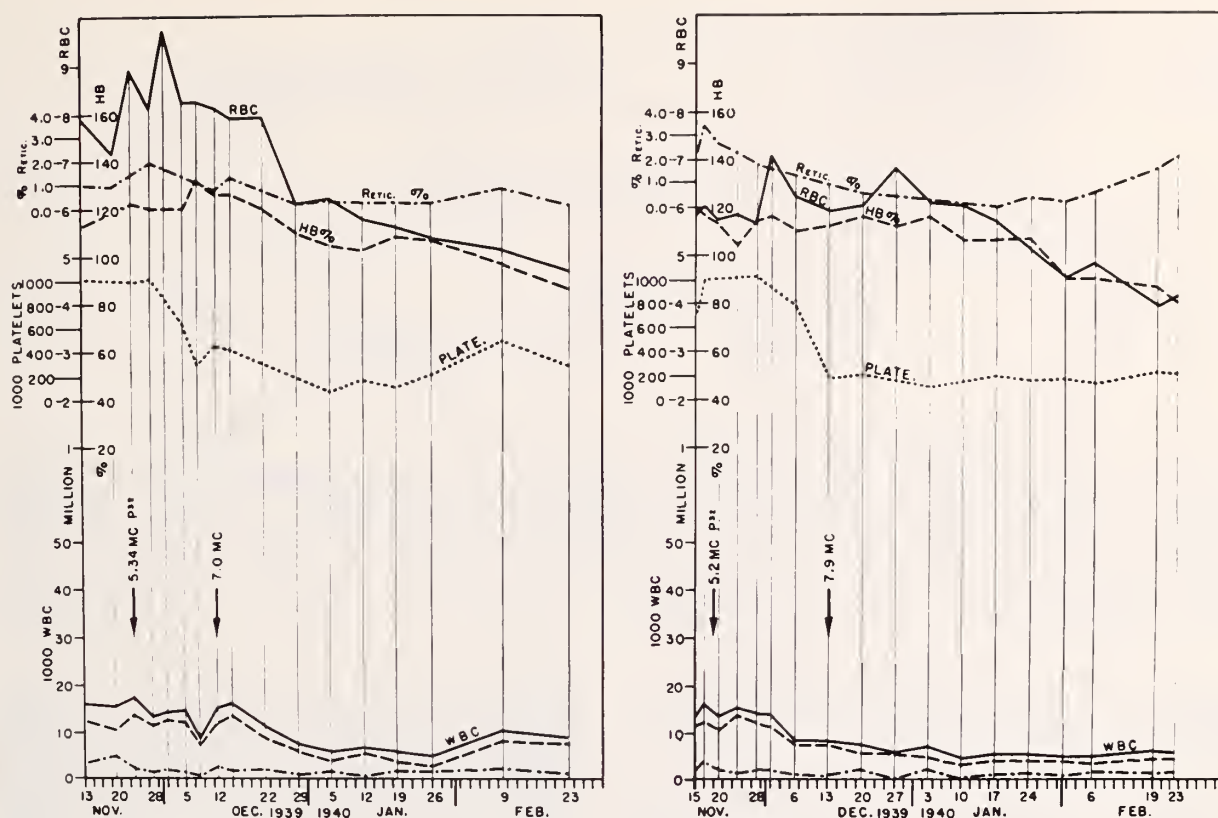


Fig. 2. Hematologic picture in 1940; two patients with polycythemia vera treated with radiophosphorus. In both patients, hemoglobin and red blood cell values fell satisfactorily, with decreases in reticulocyte count.

over of iron in the plasma, he could infer the rate of synthesis of erythrocytes. This he did by measuring the clearance of a tracer dose of radioactive iron from the blood and its subsequent appearance in circulating red cells (12). By placing scintillation counters over the liver, spleen, and pelvis, he was able to trace the movement of radioactive iron through the body (20). These studies clearly demonstrated an increased production of red cells, which was confirmed by studies reported in the *Journal of Clinical Investigation* by Wasserman and his colleagues (21).

The other principal studies on the pathophysiology of polycythemia at Berkeley were a review of the effect of treatment on the symptoms, physical findings, and changes in blood volume of treated patients (22) and studies of the changes in ferrokinetics in the course of the disease (23).

Therapeutic Use of P32. In the late 1940s, the use of P32 began to be reported—from the Mayo Clinic (24), Washington University (25), and Ohio State University (26). But not until 1953 were we, Lawrence, Berlin, and Huff, able to provide data on length of life in P32-treated patients (27); we reported a median life expectancy of 13.2 years. In 1959, Calabresi and Meyer (28) used the same statistical method of measurement

of median life expectancy as we had and reported a median life expectancy of 11 years. Wasserman and Bassen of The Mount Sinai Hospital published a comparable review in the same year (29) but did not include data on the life expectancy of P32-treated patients. In 1955, a published discussion on the treatment of polycythemia vera between Lawrence, Nathan Rosenthal (then at Beth Israel Hospital but previously at Mount Sinai), Stickney of the Mayo Clinic, and Wasserman concluded with this comment by the moderator, Dameshek: "The panel is practically unanimous in advocating P32 as the best method of therapy. However I for one still hesitate to expose an essentially normal person to the possibly delayed effects of radioactivity. Further long-term comparative studies are desirable" (30). Only by chance did I come across this discussion, because in 1955 I was in the Navy, occupied by my work at the Pentagon in the Armed Forces Special Weapons Project.

The debate, sometimes acrimonious, continued; in 1965, Frank Gardner and David Nathan convened a meeting at the Peter Bent Brigham Hospital which I chaired and which was reported in *Seminars in Hematology* in 1966 (31). This meeting did not resolve the issues, but in his in-

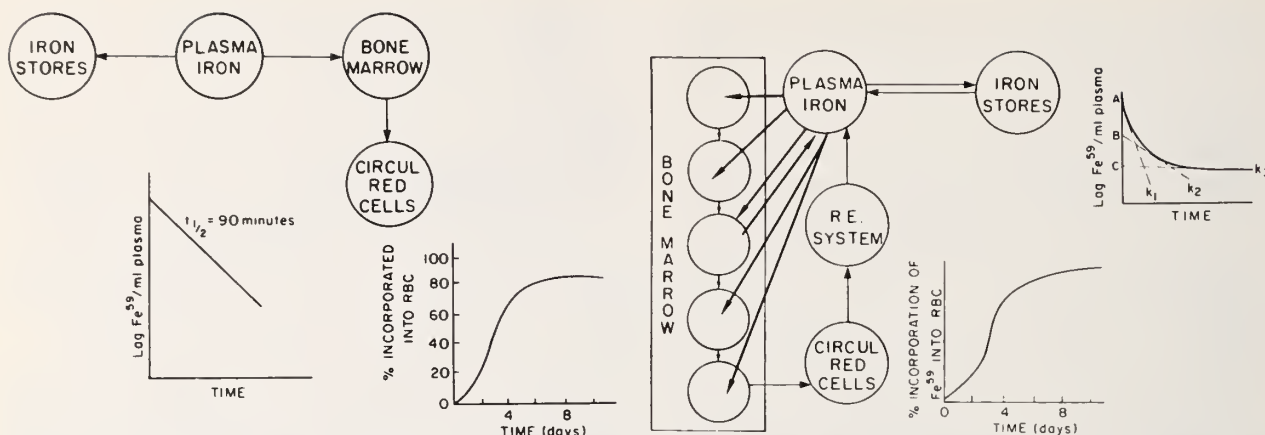


Fig. 3. Left Single dynamic pool model of iron metabolism. Radioactive iron injected into the plasma iron pool is cleared from plasma with a single exponential, and approximately 80% is incorporated into circulating red blood cells. Right Model of iron metabolism; marrow depicted as series of five compartments, with reflux to plasma from middle marrow compartment and reflux from stores. In the normal state, a system delay in return of radioactive iron from circulating red blood cells via reticuloendothelial system amounts to about 90 days and peaks at 120 days. Plasma iron clearance is described mathematically as $P_t = Ae^{-k_1t} + Be^{-k_2t} + Ce^{-k_3t}$, where $P_t = {}^{59}\text{Fe}$ per mL plasma at time t , $A + B + C = 1$, and $k_1, k_2, k_3 =$ rate constant for each exponential component.

troduction to the meeting and in his closing remarks, Frank Gardner wrote:

However, to have definitive answer, a cooperative group program is necessary to have a concurrent comparison of P32 and alkylating myelosuppressive therapy.... The medical organization is available to answer these questions and to observe and treat this disorder. The conflict of opinion regarding different therapies can be resolved by careful group observation. Although readers have been presented with treatment programs that are acceptable, I am hopeful that in a symposium 10 years from now we will be able to present data that will more completely answer these current unanswered questions.

Ten years later, we did not have a symposium, but we did publish "A report from the Polycythemia Vera Study Group" (32).

Polycythemia Vera Study Group. In the mid 1960s, Louis Wasserman conceived the idea of forming a multi-institutional cooperative group. The idea was initially supported in the form of a contract by Gordan Zubrod in his role as the scientific director for chemotherapy of the National Cancer Institute, and later by a grant that lasted 16 years. At the 1965 meeting in Boston and again at a panel discussion in 1968 at the Toronto meeting of the American Society of Hematology, it became apparent that further discussion would lead nowhere (33). Concurrently, the influence of the cooperative cancer chemotherapy groups and the randomized clinical trial as tools for answering the question, What is the best treatment of polycythemia vera? became evident.

The members of the Polycythemia Vera Study Group were recruited by Louis Wasserman.

The group began the work of drafting a protocol modeled in many respects after the randomized trials of the cooperative chemotherapy groups. In the process of writing a protocol, eligibility rules were created that defined criteria for entry into the study and led to the development of a decision tree (Fig. 4) (34), now called an algorithm, for the differential diagnosis of elevated hematocrit; the decision tree was updated in 1986 (Fig. 5) (35). The eligibility criteria posed few problems; they were published in *Seminars in Hematology* in 1976 and have since been cited at least 280 times, including 23 citations in the first 10 months of 1994.

Much more difficult than the eligibility criteria was the design of the treatment protocol. The starting point was that a P32 regimen was to be compared to a myelosuppressive chemotherapeutic drug, but the choice of agent was not easy. Several were considered; eventually, chlorambucil was chosen.

Venesection. Several members of the group argued forcefully that a third therapeutic option, venesection, should be included. That option was agreed to, albeit reluctantly by some (including me). To my way of thinking, the choice took some courage at that time, considering the available evidence. In 1962, the Danish physicians Chievitz and Thiede published in *Acta Medica Scandinavica* a paper entitled "Complications and causes of death in polycythemia vera" (36). The data were derived from a number of Danish hospitals (Fig. 6). They found a median survival of 12 years for patients treated with x-rays and a median survival of 3½ years for patients treated with phle-

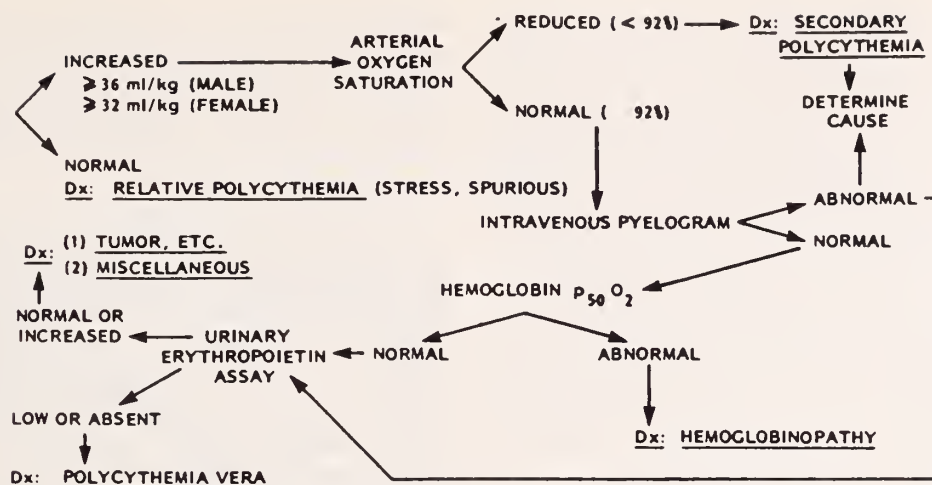


Fig. 4. Diagnostic decision tree for evaluation of elevated hematocrit, 1976.

botomy. Note that the median survival for the P32-treated patients at Berkeley was 13.2 years and, for the patients treated at the University of Wisconsin by Calabresi and Meyer, 11 years. Calabresi and Meyer wrote that their result "represents an improvement over figures reported with therapeutic methods other than P32 administration" (28). Nevertheless, Conley of Johns Hopkins and Dameshek, formerly of Tufts but at that time at The Mount Sinai Hospital and the

editor of *Blood*, maintained that their patients treated by venesection "did well," but neither furnished the data to support that contention.

Thus a three-armed randomized trial was begun, with participation by American, French, Swedish, and Israeli investigators. More than 450 patients were entered into the study. What have we learned from it? Is there a single clearly superior treatment regimen? Based on median life expectancy, the answer is no (35), although ob-

Algorithm for Evaluation of an Elevated Hematocrit

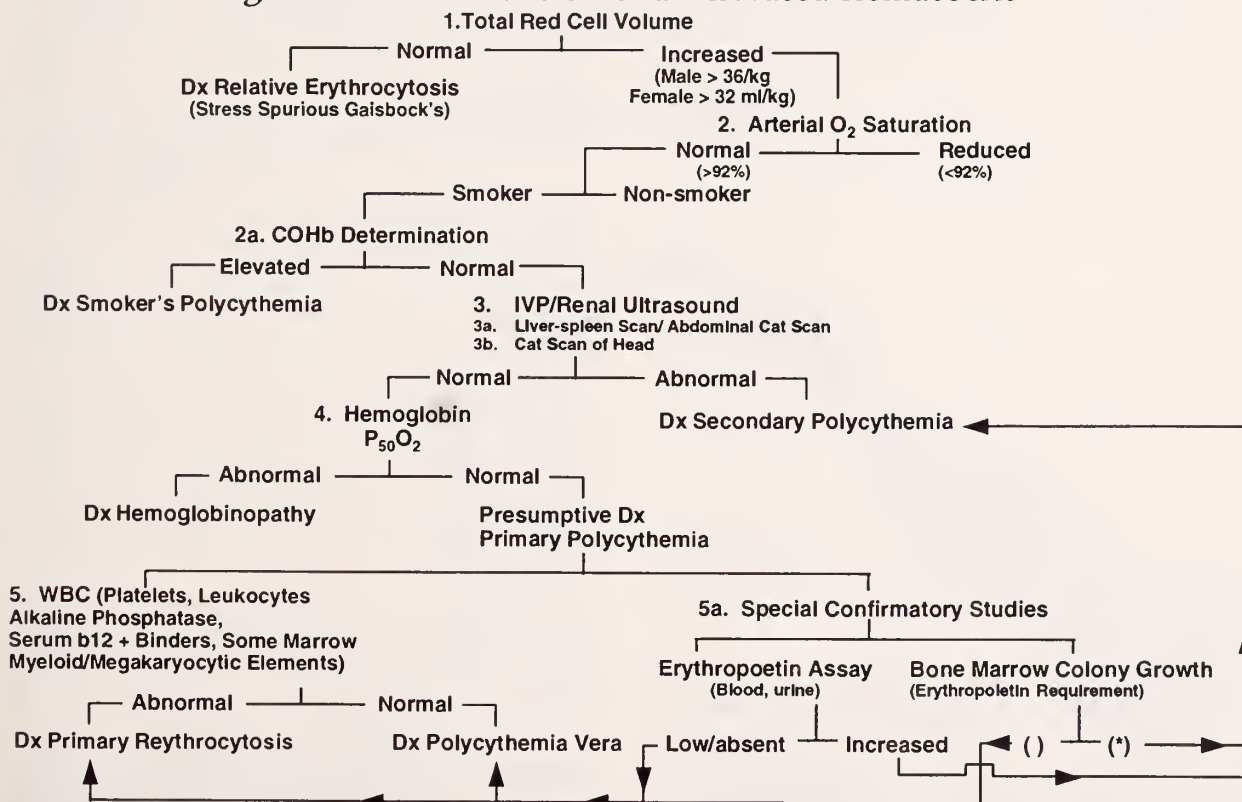


Fig. 5. Diagnostic algorithm, 1986.

served survival in the P32-treated patients was greater than or equal to that of phlebotomy-treated patients, particularly for the first 8 to 9 years after the start of treatment (Fig. 7). Spanish hematologists have recently reported that the life expectancy of Spanish patients falls within the range of normal life expectancy of an age- and sex-matched Spanish population (48) (Fig. 8), a comparison we did not make. Chlorambucil proved to be a leukemogen, and its use was stopped by 1981 (37). Acute leukemia is a prominent cause of death in P32-treated patients, and vascular complications are a prominent cause of death in phlebotomy-treated patients, particularly in the first two years of treatment.

Other therapeutic studies have added to our knowledge. The combination of aspirin and persantine did not prevent thrombosis and hemorrhage in phlebotomy-treated patient and was discontinued (38), but the dose of aspirin was greater than would be used today. Hydroxyurea was studied (39), and today constitutes the most common treatment modality, if not the treatment of choice if myelosuppression is desired, although hydroxyurea may be a leukemogen (40).

Powers Peterson and John Ellis of Cornell have described in wonderful detail the architecture and cytology of the bone marrow (41, 42) and at Mount Sinai, Zanjani added to our diagnostic armamentarium the fact that bone marrow put into culture from polycythemia vera patients did not require erythropoietin for erythroid colony growth (43). This 1977 work led to a number of studies that are beginning to unravel, at the molecular biology level, the pathophysiology of polycythemia vera, which began with the demonstration in 1976 that polycythemia vera is a clonal disorder (44).

On the therapeutic side, Richard Silver of Cornell, who is a member of the Polycythemia Vera Study Group, has shown that interferon-2 alpha can produce remission (45). This has been confirmed, and interferon alpha has been reported to be an effective treatment of the pruritus that plagues many patients (46).

Data on Survival. In the 1987 update of survival data (47), median survival is 10.9 years for P32-treated patients, 9.1 years for chlorambucil-treated patients, and 12.6 years for phlebotomy-treated patients (Fig. 7).

Therapeutic Recommendations. Patients over the age of 70 are most effectively treated with radioactive phosphorus and supplemental phlebotomy. Patients younger than 50 years of age, and particularly women in their child-bearing years, should be managed with phlebotomy

alone, unless specific thrombosis-associated risk factors are present. Myelosuppression with hydroxyurea seems advisable in such younger patients if they have a high (more than 3–4 per year) phlebotomy requirement or a history of a prior thrombotic event.

The role of myelosuppression is most uncertain in the age group between 50 and 70 years. In the physiologically young patient in this age group, in the absence of thrombosis-associated risk factors, management by phlebotomy alone is possible. If myelosuppression is advisable, hydroxyurea appears to be the current agent of choice. Excessive splenic enlargement accompanied by local symptoms, bone tenderness, intractable pruritus, or difficult venipuncture may be other indications for myelosuppression.

The hazard of a markedly elevated platelet count has been much discussed. In this context, recommendations based on Polycythemia Vera Study Group protocols (35) have this to say:

Although extensive statistical analysis has failed to associate an elevated platelet count with a high risk of thrombotic complications, many physicians undoubtedly will continue to believe that a substantial increase in platelet count requires myelosuppression. We would emphasize that this belief is not supported by any of the data of the PVSG studies.

The demonstration, which began at Mount Sinai, that the bone marrow of patients with polycythemia vera contains progenitor cells that give rise to erythroid colonies and do not require added erythropoietin in the culture medium for growth has been followed by further studies that have become part of the diagnostic algorithm. Perhaps the most recent is a 1994 paper by Correa, Eskinnazi, and Axelrad (49) on the hypersensitivity of circulating erythroid progenitors in polycythemia vera to insulin-like growth factor. An editorial accompanying that paper, on the implications of the cellular defect in polycythemia vera for clinical diagnosis and molecular pathophysiology, appropriately suggests that these erythroid progenitors could be used to create a diagnostic test (50). Studies of the erythropoietin receptor in polycythemia vera show that it appears to be normal (51–53), although it is truncated in familial erythrocytosis (50).

Najean and his colleagues have recently published a short report indicating that in France, patients treated with phlebotomy alone are difficult to maintain (54). In 1955, Lou Wasserman wrote the following (30):

Patients with erythemia treated by repeated venesections so as to induce iron deficiency become severely incapacitated and "polycythemic cripples" of little use to themselves

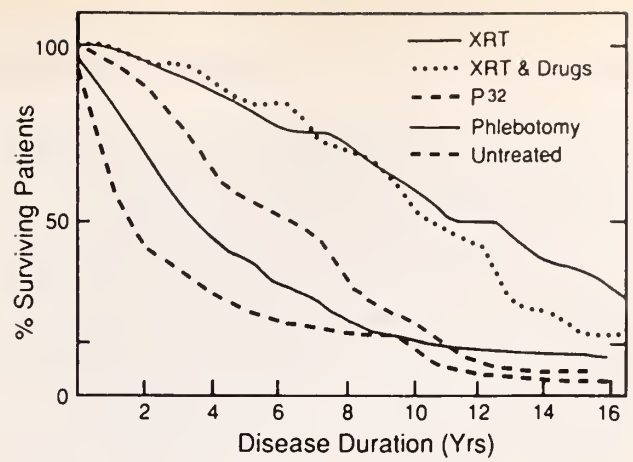


Fig. 6. Median survival reported in 1962 for patients not treated and those treated with x-rays, P32, phlebotomy. Adapted from ref. 36.

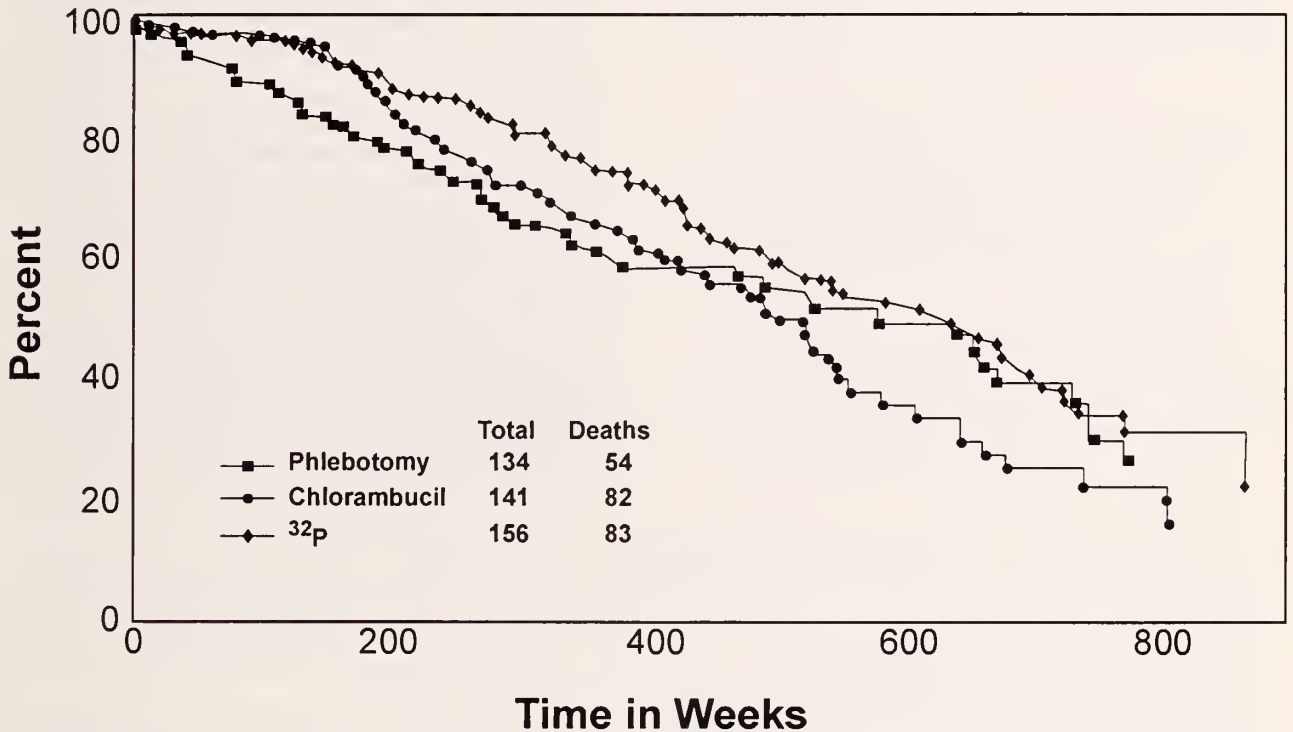


Fig. 7. Cumulative survival, percentage of patients treated with P32, chlorambucil, and phlebotomy, Polycythemia Vera Study Group-01. Adapted from ref. 47.

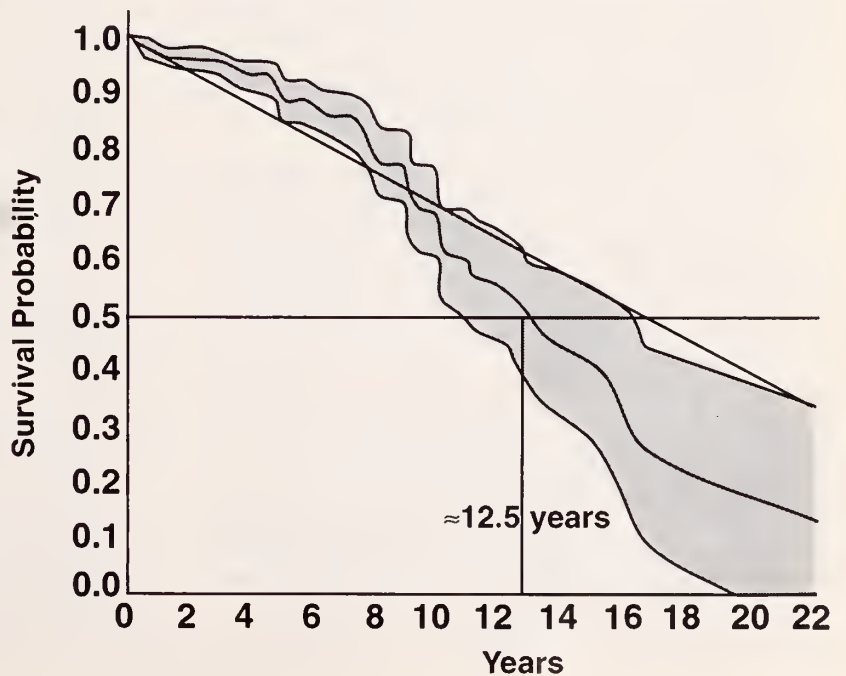


Fig. 8. Life expectancy of 454 Spanish patients with polycythemia vera. Shaded area, 95% confidence limits. Actuarial survival is shown in line between confidence limits. Survival of age- and sex-matched control population is depicted in straight diagonal line. Adapted from ref. 48.

or their families. . . . The fundamental disturbance in polycythemia is the marrow panmyelosis due perhaps to neoplastic stimulation of the primitive reticulum cell.

I hope this glimpse into the history of the development of knowledge of polycythemia vera and the interrelationships of John Lawrence, Louis Wasserman, and myself has been rewarding. Those relationships began for me in 1947 at Berkeley and have continued throughout our lives (55), although Lawrence's death left only Lou and myself. I owe much to Lou; we all owe much to him for his contributions to hematology.

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Listeria monocytogenes Infections:

Laboratory Investigation of an Unexpected Increase in Incidence

EDWARD J. BOTSTONE, PH.D., AND HASSAN NAMDARI, PH.D.

Abstract

Listeria monocytogenes is a facultative intracellular pathogen causing mainly meningitis and septicemia in immunocompromised hosts. From July 1988 through December 1989, 16 patients at The Mount Sinai Hospital were diagnosed as having listeriosis shortly after admission, 14 within a one-year period (July 1988–July 1989). Because this incidence was almost double the incidence in previous years (<8 annually), an epidemiologic and microbiologic investigation was undertaken to determine a potential route of acquisition of *L. monocytogenes*. On the basis of plasmid profile, bacteriocin (enterocin) susceptibility pattern, and serotype, no single epidemic strain could be identified. Although direct evidence was lacking, we concluded that our patients may have acquired *L. monocytogenes* through transient contamination of food.

LISTERIA MONOCYTOGENES, a gram-positive pleomorphic bacillus, causes a diverse array of human infections, most frequently in the setting of a pre-existing underlying disease (1, 2). Infection may occur sporadically, or in epidemic clusters usually attributable to a food source (3, 4).

L. monocytogenes is classified as a facultative intracellular pathogen capable of invading and multiplying within a wide range of host cells (corneal, conjunctival, pulmonary), including macrophages. Infection with *L. monocytogenes* ensues after consumption of foods such as salads, meats, and raw or inadequately pasteurized dairy products contaminated with the microorganism (1). *L. monocytogenes* grows well at 4° C and is tolerant of high salt concentration and of the food preservative sodium nitrate, all of which favor its growth in food products (6). Contamination of

foods is a consequence of its widespread distribution in the environment (vegetation, soil) and in animals (mammals, birds, fish) (6).

Subsequent to ingestion, invasion of intestinal epithelial cells is the key virulence attribute of *L. monocytogenes* and is mediated through an 80 kDa surface protein termed internalin (7). Once the organism is internalized in a phagosome, low iron concentration induces synthesis of listeriolysin O, a hemolysin which disrupts the phagocytic membrane, allowing *Listeria* to escape into the cell cytoplasm (8). Through a surface protein on the bacterium, actin filaments are polymerized on the bacterium, forming a "tail" propelling the bacterium through the host cell and into adjacent cells (9).

After replication in nonphagocytic host cells, *Listeria* are phagocytized by inflammatory macrophages through complement receptor (CR3) which binds to C3 deposited on the bacterial surface (10). Within the macrophage, *Listeria* again escapes the phagosome to enter the macrophage cytoplasm and continues to replicate using host cell nutrients. Actin assembly on the bacterium's surface propels it to the macrophage membrane, where a protuberance (pseudopod) is formed (11).

From the Division of Infectious Diseases, The Mount Sinai Hospital, One Gustave L. Levy Place, Box 1122, New York, NY 10029-6574.

Address requests for reprints to the first author there. The current address of the second author is Clinical Laboratories, Inc., 441 Wyoming Avenue, Scranton, PA 18509.

Contact with a neighboring macrophage results in phagocytosis of the pseudopod containing *Listeria*. Escape from the second macrophage phagosome repeats the cycle. In this fashion, *L. monocytogenes* perpetuates an intracellular existence. Control of *L. monocytogenes* infection is ultimately achieved through the activation of macrophages after antigen presentation through the major histocompatibility complex type 1 (MHC class 1) by infected monocytes to CD8⁺ T lymphocytes, and generating cytotoxic T lymphocytes to kill *Listeria*-infected cells (12).

At The Mount Sinai Hospital during the period from July 1988 through December 1989, 16 patients were diagnosed as having listeriosis shortly after admission, 14 within a one-year period (July 1988–July 1989), and 9 within a four-month period (July–November 1988). Because *L. monocytogenes* is infrequently isolated from this hospital's patient population—for example, 8 isolates in 1987—the increased and clustered isolation of *L. monocytogenes* prompted an evaluation of the risk factors and epidemiologic correlates that could have accounted for the heightened incidence. Concurrently, we studied 10 of the 16 outbreak isolates available by assessing their

plasmid profile, bacteriocin (enterocin) susceptibility pattern, and serotype.

Materials and Methods

Twelve of the 16 *L. monocytogenes* isolates were derived from the blood and one each from cerebrospinal fluid, pleural fluid, amniotic fluid, and perirectal abscess of patients admitted to The Mount Sinai Hospital. Nine of these isolations were made during the four-month period from July 28, 1988 through November 30, 1988 (Table 1). For comparative purposes, three available *L. monocytogenes* strains isolated in 1987 were also studied.

Each of the isolates was characterized as *L. monocytogenes* on the basis of its microscopic morphology (gram-positive cocci and bacilli), production of beta-hemolytic colonies on 5% sheep blood agar, and positive cAMP reaction using *Staphylococcus aureus* beta lysin, catalase production, and motility at 25° C. The isolates fermented salicin, glucose, rhamnose, and trehalose, hydrolyzed esculin, and gave a positive Voges-Proskauer reaction. Tests for nitrate reduction and urease activity were negative.

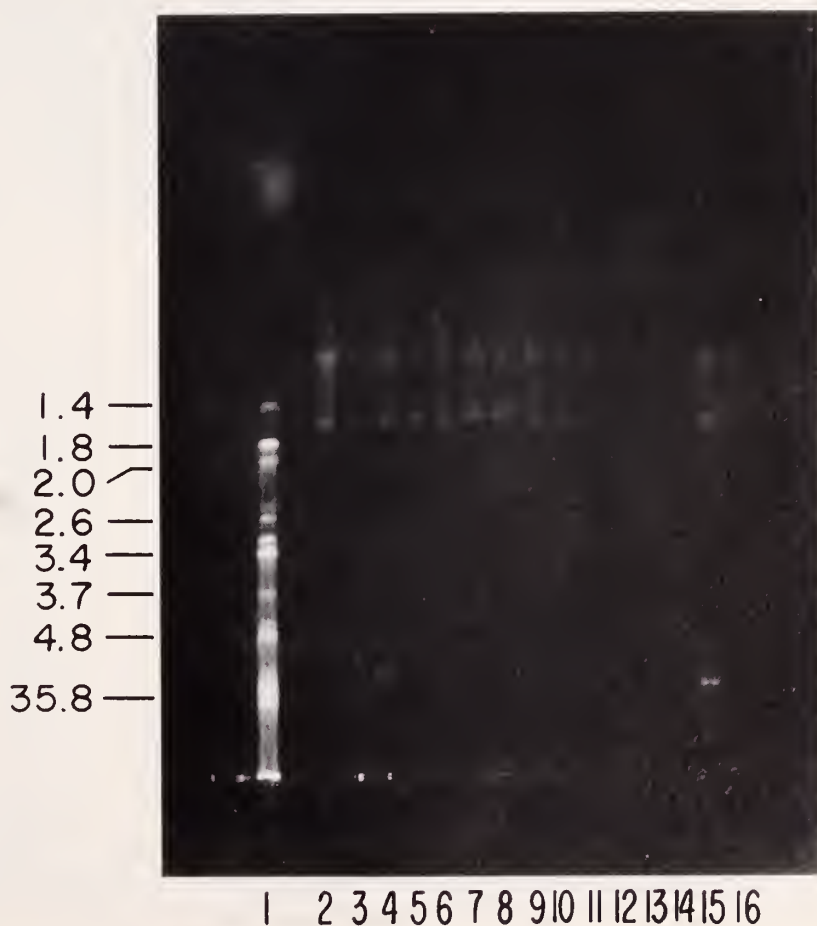


Fig. Ethidium bromide-stained agarose gel of control plasmid DNA of *Escherichia coli* V517 (lane 1) and 15 clinical isolates of *Listeria monocytogenes* (lane 2–16). All *L. monocytogenes* isolates except one (lane 12) share 3 plasmids (36 kb, 1.5 kb, 2 kb).

Plasmid profiling of 10 of the *L. monocytogenes* strains and the three strains isolated in 1987 was undertaken by the method of Birnboim (13). Plasmids were isolated by rapid alkaline extraction and subjected to gel electrophoresis on 0.7% agarose. A multiple plasmid-containing strain of *Escherichia coli* provided by Barbara Backman was used as a referral for plasmid size (14).

Bacteriocin typing of 10 of the 16 *L. monocytogenes* and of the three 1987 isolates was assessed by susceptibility or resistance to the bacteriocin of two strains of *Enterococcus faecalis* var *zymogenes* and one *E. faecium* (15). Briefly, confluent lawns of each *L. monocytogenes* strain were prepared, after which the three bacteriocin-producing enterococcal strains were spotted on the lawn surface. Plates were incubated at 35°C and examined after 18 h for a zone of inhibition around the spot inoculum.

Serotyping of 9 of the 16 isolates was performed through the courtesy of P. S. Hayes of the Centers for Disease Control (CDC), Atlanta, GA.

Results

From July 1988 through December 1989, 16 isolates of *L. monocytogenes* were recovered which traversed the usual clinical spectrum of infections with this species (Table 1). Nine of these isolates were recovered from individual patients within four months, 14 within a one-year period. In each of four of the months during the period (July 1988, Sept. 1988, Nov. 1988, July 1989), either two or three patients with listeriosis were hospitalized. There was, however, no evidence of

nosocomial spread within the institution; these patients were geographically separated within the hospital and each had clinical symptoms and a medical condition either predisposing to or known to be associated with listeriosis (Table 1).

Plasmid profiling showed that 9 of 10 *L. monocytogenes* strains isolated during the period of heightened incidence and three isolates recovered in 1987 carried three similar plasmids, 1.5 kb, 2 kb, and 36 kb respectively (Fig.). The remaining isolate, recovered in October 1989, had no demonstrable plasmids.

All 10 *L. monocytogenes* isolates, as well as the three isolates from 1987, were inhibited by the three bacteriocinogenic enterococcal strains, as indicated by a distinct zone of inhibition around the spot inoculum. Bacteriocin susceptibility was not related to serotype.

Serologically, of 9 of the 16 outbreak isolates submitted to the CDC for typing, 5 were serotype 4b; 3 were serotype 1,2b; and one was serotype 1,2a. Two of the three 1987 isolates were serotype 1,2; the third was serotype 4b.

Discussion

During the past decade in the United States and Canada, five major outbreaks of listeriosis have occurred; all were either directly (3–5) or epidemiologically (16, 17) linked to food. Interestingly, each of the outbreaks involved individuals geographically dispersed over a large area and hospitalized in several facilities. In two outbreaks, for instance, 23 patients in eight Boston hospitals in a two-month period (16) were identi-

TABLE 1
Isolation of *Listeria monocytogenes* at The Mount Sinai Hospital July 1988 through December 1989

Month and year	No. of isolates	Source	Serotype	Comments
July 1988	2	Blood	ND	Cerebritis; steroids for IFBD
		Blood	ND	AIDS
Sept. 1988	3	Blood	ND	AIDS
		Blood	ND	AIDS
		Pleural	4b	Congestive heart failure
Nov. 1988	4	Blood	4b	IFBD, steroids
		Blood	4b	Pregnancy
		Blood, CSF	ND	AIDS
		Blood	1,2b	Newborn
Jan. 1989	1	Blood	1,2a	AIDS
April 1989	1	CSF	4b	Newborn
July 1989	3	Amniotic fluid	4b	Pregnancy
		Perirectal abscess	1,2b	Perirectal abscess
		Blood	1,2b	Diverticulitis
Oct. 1989	1	Blood, CSF	ND	Lymphoma
Dec. 1989	1	Blood	ND	Carcinoma

ND, not done; CSF, cerebrospinal fluid; IFBD, inflammatory bowel disease.

fied as having listeriosis and 36 patients in several hospitals in the metropolitan Philadelphia area were so identified during a four-month period (17). By way of contrast, all 16 of the patients in the series reported here were hospitalized at The Mount Sinai Hospital. Because telephone calls to the microbiology directors of several major New York City institutions, including Memorial Sloan-Kettering Hospital, Kings County Hospital, and Columbia-Presbyterian Hospital, did not reveal an increased incidence of *Listeria* isolation at their institutions, the heightened isolations at our facility were surprising and therefore investigated.

As in previously reported outbreaks of listeriosis, our patient population spanned the range of susceptible individuals, including those with acquired immunodeficiency syndrome or malignancy, those who were pregnant, and those receiving immunosuppression therapy for inflammatory bowel disease. Other associated conditions included congestive heart disease, diverticulitis, and perirectal abscess.

There was no apparent outbreak of listeriosis in the New York City area between July 1988 and November 1988, when we encountered 9 patients with *L. monocytogenes* infection, a number surpassing the institution's isolation rate of 8 for all of 1987. Unlike the outbreak described by Ho et al. (16), however, careful investigation of the clinical records, time of admission, and assigned medical service did not support nosocomial spread of *Listeria* within the institution to account for the increased incidence. In fact, these 16 patients were all symptomatic on admission and were diagnosed with listeriosis shortly after admission by culture of blood or other body fluid.

Epidemiologically, we attempted to further characterize the *L. monocytogenes* isolates through plasmid profiling, bacteriocin susceptibility pattern, and serotyping. With the exception of a single isolate recovered in October 1989 that was devoid of any plasmids, nine strains isolated during the period of heightened occurrence and three from 1987 all possessed three identical plasmid species and showed an identical bacteriocin susceptibility pattern. These data alone would support a single infecting strain among our patient population and, although data were unavailable from other New York City hospitals, perhaps even in the greater New York City area. Alternatively, as several serotypes were recorded among our *L. monocytogenes* isolates (Table 1), the similarity in the plasmid profile and bacteriocin susceptibility pattern suggests that these are common rather than distinguishing markers of *L. monocytogenes*. An expansion of the spectrum of

bacteriocin-producing enterococcal strains active against *L. monocytogenes*, phage (18) and isoenzyme typing (19), however, might have allowed better discrimination of the isolates.

We have no clear-cut hypothesis to account for the increased incidence of listeriosis at the institution from July to November 1988 or for the entire period from July 1988 to December 1989. It is possible that the observed increase in incidence represents the chance clustering of susceptible individuals who were admitted to the hospital. This thought is provocative, and is substantiated by several facts: neither our patient population nor our blood or spinal fluid culture procedures had changed appreciably during the five years preceding the increased incidence, and only 8 *L. monocytogenes* isolates were found during all of 1987. Further, in the period from December 1989 through December 1994, only 9 isolates of *L. monocytogenes* were found. This apparent decrease in the incidence of human listeriosis may be attributed to tighter monitoring techniques for foodstuffs and dietary recommendations for preventing food-borne listeriosis (20).

Could our patients have acquired *L. monocytogenes* de novo from contaminated food or could a latent gastrointestinal tract colonization have been activated because of an underlying predisposing condition such as pregnancy or AIDS or the use of steroids? Because data were not available and the increased incidence was seemingly restricted to our institution only, we have no epidemiologic proof of a widespread food-borne outbreak of listeriosis in the New York City area. Additionally, since the recognized outbreak, cultures of 600 stool specimens performed to identify *L. monocytogenes* carriage among symptomatic and asymptomatic persons at our institution have not revealed *L. monocytogenes*. Instead, we have recovered two isolates of *L. welshimerii*.

The outbreak at The Mount Sinai Hospital bears a similarity to that reported by Schwartz et al. (17), who documented an increased incidence of *Listeria* infection in the Philadelphia metropolitan area caused by different serotypes of *L. monocytogenes*. They concluded, as we have, that although no single epidemic strain could be identified, an outbreak or increased incidence did occur. Because one-third of the patients comprising the Philadelphia outbreak had vomiting and diarrhea, Schwartz et al. (17) postulated that asymptomatic gastrointestinal tract carriage of *L. monocytogenes* could have resulted in disseminated disease by a co-infecting microorganism that altered the integrity of the gastrointestinal mucosa. Perhaps this scenario could also account

for the focalized increase in incidence of listeriosis at our institution.

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Improving Patient-Controlled Analgesia:

Adding Droperidol to Morphine Sulfate to Reduce Nausea and Vomiting and Potentiate Analgesia

GORDON M. FREEDMAN, M.D., JOEL M. KREITZER, M.D., SCOTT S. REUBEN, M.D., AND JAMES B. EISENKRAFT, M.D.

Abstract

Opioid-related side effects, including nausea and vomiting, are common in patients using morphine in patient-controlled analgesia for postoperative pain relief. The purpose of this study was to determine if the addition of droperidol to a morphine sulfate delivery system could decrease the incidences of nausea and vomiting without increasing droperidol-related side effects. Forty ASA 1 and 2 patients scheduled to undergo peripheral orthopedic surgery were randomized to receive either morphine sulfate (2 mg/mL), or morphine sulfate (1.9 mg/mL) plus droperidol (0.125 mg/mL) for postoperative self-controlled analgesia. Visual analogue scores for pain, nausea, and sedation were obtained from each patient immediately after surgery and each morning and evening until patient-controlled analgesia was discontinued approximately 48 hours later. Total patient-controlled use of morphine sulfate was recorded at each visual analogue rating. The patients who used morphine sulfate plus droperidol had significantly less nausea and vomiting and used significantly less morphine. No patient experienced droperidol-related side effects. We conclude that the routine addition of droperidol to morphine sulfate in self-controlled analgesia improves the comfort of patients following peripheral orthopedic surgery.

PATIENT-CONTROLLED ANALGESIA (PCA) is commonly used for providing postoperative pain relief. Opioids are the analgesic drugs most frequently administered using PCA systems. Problems that can occur with PCA are few and those that do occur are usually related to operator or patient error or to mechanical problems (1).

Potential side effects associated with the use of intravenous opioids include respiratory depression, pruritus, sedation, nausea, and vomiting.

Since patients receiving opioids by PCA require a smaller total dose of opioid than with traditional delivery systems and maintain opioid blood levels at much more constant concentrations within the therapeutic window, the incidence of such side effects should be decreased. In patients who use morphine sulfate PCA systems, however, nausea and vomiting continue to be problematic and have been reported to occur in up to 30% of such patients (3).

A recent study has shown that the addition of promethazine to PCA morphine sulfate decreases nausea and vomiting (4). The present study was undertaken to determine if the addition of droperidol, an antiemetic commonly used perioperatively, to a PCA morphine sulfate system decreases the incidence of nausea and vomiting without causing a significant incidence of droperidol-related side effects in patients who have undergone orthopedic limb surgery under general anesthesia.

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From the Department of Anesthesiology, Mount Sinai School of Medicine (CUNY), New York, NY 10029.

Address reprint requests to Dr. Freedman, Assistant Professor, Department of Anesthesiology, Mount Sinai School of Medicine, Box 1010, One Gustave Levy Place, New York, NY 10029-6574.

TABLE 1

Demographic Data, Patient-Controlled Analgesia with Morphine Sulfate (Controls) and Morphine Sulfate plus Droperidol (Study Patients)

	Control N = 20	Study N = 20
Age (yr)	48 ± 19	50 ± 19
Sex (M/F)	11/9	9/11
Weight (kg)	75 ± 17	76 ± 17
Height (cm)	168 ± 11	167 ± 11
Anesthesia time (hr)	3.8 ± 1.4	4.1 ± 1.8
Intraoperative fentanyl (mcg)	415 ± 188	453 ± 281
Duration of PCA use (hr)	49 ± 10	44 ± 10

TABLE 2

Nausea Ratings, Visual Analysis Scale (VAS), over Time during Patient-Controlled Analgesia

Hours	Nausea VAS Rating					
	Control	(range)	N	Study	(range)	N
12	1.5	(0–5.9)	20	0.2	(0–8.9)	20
24	0.8	(0–9.4)	20	0.0	(0–5.0)*	20
36	0.1	(0–6.4)	19	0.0	(0–8.2)	19
48	0.2	(0–6.6)	16	0.0	(0–0.7)*	11
60	0.0	(0–3.9)	7	0.0	(0–1.0)	3
Median	0.8	(0–5.7)	20	0.3	(0–3.7)*	20

N values decrease with time as patients in whom PCA became unnecessary discontinued it.

* $P < 0.05$ between-group comparisons.

TABLE 3

Median Sedation VAS Ratings over Time during Patient-Controlled Analgesia

Hours	Control	(range)	N	Study	(range)	N
12	5.3	(2.0–9.8)	20	5.5	(0.2–9.2)	20
24	3	(0.1–9.0)	20	5.1	(0.0–9.5)	20
36	2	(0.0–8.6)	19	5.2	(0.0–9.7)	19
48	2.1	(0.0–8.4)	16	3.7	(0.0–10.0)	11
60	2.7	(0.4–6.5)	7	0.4	(0.3–8.3)	3
Median	3.5	(0.7–7.4)	20	4.3	(1.5–8.5)	20

Materials and Methods

After approval of the protocol by the Institutional Review Board of the Mount Sinai Medical Center, 40 patients classed as American Society of Anesthesiologists physical status 1 or 2 and scheduled to undergo orthopedic surgery of an extremity were studied. The sample size was determined by power analysis. All gave their written informed consent to participate. Exclusion criteria included history of Parkinson's disease, neurologic dysfunction, anxiety disorder, gastrointestinal disease, chronic pain syndrome, opioid abuse, or known allergy to morphine sulfate or droperidol. All patients had preoperatively de-

cided to use PCA as their method of postoperative pain relief and each was randomized to receive either PCA with morphine sulfate (2 mg/mL) (control group) or PCA with morphine sulfate (1.9 mg/mL) plus droperidol (0.125 mg/mL) (study group). Preoperatively the patients received either oral diazepam (5–10 mg) or intravenous midazolam (1–2 mg). General anesthesia was induced with thiamylal sodium (up to 5 mg/kg) followed by succinylcholine (1 mg/kg) and tracheal intubation. Anesthesia was maintained with fentanyl (up to 6 mcg/kg), N_2O/O_2 (70%/30%), and isoflurane (end-tidal concentrations of up to 1.2%). No prophylactic antiemetics were given intraoperatively. Neuromuscular block was achieved with vecuronium, and residual relaxation was antagonized with neostigmine and glycopyrrolate, allowing immediate postoperative tracheal extubation.

PCA was started in the postanesthesia care unit. The infusion pump (Bard PCA I, Bard Medical Systems, North Reading, MA) settings were: a demand dose of 0.7 mL (morphine sulfate 1.40 mg, control group; morphine sulfate 1.33 mg plus droperidol 0.09 mg, study group); a lockout period of 8 minutes; and a continuous infusion of 0.5 mL/hour (morphine sulfate 1.0 mg/hour, control group; morphine sulfate 0.95 mg/hour and droperidol 0.06 mg per hour, study group). Following the routine of our Pain Management Service, the continuous infusion was discontinued after the first night, and demand doses and lockout intervals were adjusted as necessary. The PCA was discontinued when patients had adequate analgesia and were tolerating oral intake of analgesics.

Visual analogue scores for pain, nausea, and sedation were obtained by having the patient indicate severity on a 10-cm visual analogue scale (VAS) immediately after the surgery and each morning and evening (approximately every 12 hours) until the PCA was discontinued. The patients gave each parameter a score on a scale that ranged from least, 0 cm, to worst, 10 cm. A group median score was also calculated from each set of VAS data. This was the median of the average scores of each patient in that group over the entire study period. Total PCA volumes, as determined from the PCA pump computer memory, were recorded at each VAS rating. The number of patients in each group who vomited at any time during the study period was recorded. Intravenous prochlorperazine 10 mg was available on request to all patients for severe nausea or vomiting. Any opioid- or droperidol-related side effect was noted after questioning the patients on daily

rounds. Vital signs for each patient, including blood pressure, heart rate, and respiratory rate, were recorded every 8 hours. Both the patient and the investigator asking the patient to provide the VAS ratings were blinded as to the patient's treatment group.

Unless otherwise stated, data are presented as the median; the range is given in parentheses. The demographic data are expressed as the mean $\pm$ standard deviation. Median VAS scores for pain, nausea, and sedation for the two groups were compared using the Mann-Whitney rank sum test, and mean demographic data were compared by Student *t* test for unpaired data. The incidence of vomiting in each group was recorded using the chi square test with continuity corrections. $P < 0.05$ was considered statistically significant.

Results

The patient groups were similar with respect to age, weight, height, sex, anesthesia time, amount of intraoperative fentanyl administered, and total duration of PCA use (Table 1). The operative procedures in the study and control groups were similar. For the study group, the procedures included 8 total hip replacements; 3 total knee replacements; 3 internal fixations of the lower extremity; 2 leg tumor resections; 2 ankle arthrotomies; 1 elbow arthrotomy; and 1 leg amputation. For the control group, the procedures included 7 total hip replacements; 4 total knee replacements; 5 internal fixations of the lower extremity; 2 leg tumor resections; 1 shoulder repair; and 1 arm amputation.

The patients in the study group had a significantly lower group median VAS nausea rating than the control group (0.3 vs. 0.8, $P < 0.05$) (Table 2). The median 24-hour and 48-hour ratings were significantly lower as well. There was also a significantly lower incidence of vomiting in the study group. Of 20 patients in the control group, 10 vomited (50%), compared with only 3 of 20 in the study group (15%, $P < 0.05$).

No statistically significant difference was found when comparing the group median VAS sedation ratings of the control and study groups (3.5 vs. 4.3) (Table 3). The mean dose of droperidol used in the study group was 3.8 mg. No patients experienced droperidol-related side effects such as hypotension, extrapyramidal symptoms, anxiety, or restlessness, and only one patient who received droperidol plus morphine sulfate felt subjectively lethargic enough to request a discontinuation of the PCA system.

TABLE 4
Median Pain VAS Ratings over Time during Patient-Controlled Anesthesia

Hours	Control	(range)	N	Study	(range)	N
12	4.4	(4.0–9.5)	20	4.1	(0.5–9.4)	20
24	3.4	(0.3–9.8)	20	2.5	(0.2–7.5)	20
36	2.1	(0.0–7.3)	19	1.8	(0.0–9.5)	19
48	1.5	(0.0–6.6)	16	2.4	(1.0–8.4)	11
60	1.3	(0.8–7.9)	7	2.5	(0.2–5.2)	3
Median	3.1	(0.5–6.2)	20	3.0	(0.9–7.5)	20

TABLE 5
Median Cumulative Morphine Sulfate Used (mg) over Time (hours) during Patient-Controlled Analgesia

Hours	Control (range) N = 20	Study (range) N = 20
12	35 (5–120)	27 (8–90)
24	58 (19–192)	43 (20–102)
36	70 (24–260)	52 (21–125)*
48	87 (24–280)	53 (21–125)*
60	96 (24–332)	54 (21–125)*

* $P < 0.05$ between-group comparisons.

We did not find a significant difference between the group median VAS pain scores (3.0 for the study group vs. 3.1 for the control group) (Table 4). The study group, however, used significantly less morphine sulfate to obtain these same pain scores (54 mg for the study group vs. 96 mg for the control group, $P < 0.05$) (Table 5).

Discussion

Patient-controlled analgesia (PCA) has been shown to be an efficient and effective way of relieving acute postoperative pain. Compared to intramuscular analgesic regimens, it maintains more constant opioid blood levels and a longer period in which those levels are above the necessary therapeutic analgesic plasma threshold (5). PCA has been shown to provide better analgesia with less opioid use than intramuscular analgesia delivery systems (2, 6). Patients using PCA demonstrate improved pulmonary function (2, 7), a decrease in postoperative pulmonary complications (2, 7), earlier postoperative ambulation (8), and shorter hospital stays and costs (2, 8).

The major complications of PCA encompass the general side effects of the opioids used. Although the PCA system entails intrinsically fewer postoperative complications than does intramuscular opioid delivery, further decrease in PCA opioid side effects remains the objective.

Studies have reported nausea and vomiting rates of 10%–30%, depending on the type of sur-

gery undergone, in patients using morphine PCA (1, 3). The 50% incidence of vomiting in the control group of the study reported here may be attributable to the fact that all the patients started oral intake on the evening of the day of surgery. Following intraabdominal surgery, patients usually do not start eating so soon and possibly even have nasogastric tubes in place; this would confound the observations on nausea and vomiting.

Compared with the control group, the study group had significantly lower subjective feelings of nausea as rated by visual analogue scores. Also, fewer patients in the study group vomited. All of the patients who vomited requested and received prochlorperazine, and in these cases only one dose was needed to rid the patient of nausea.

Postoperative nausea may have many causes, including anesthetic-analgesic drugs, surgical manipulation, and pain. We attempted to exclude the surgical causes by studying patients undergoing nonabdominal procedures on an extremity. Anesthetic-analgesic drugs may cause nausea by stimulation of dopaminergic receptors in the chemoreceptor trigger zone of the medulla of the brain. Activation of this zone results in efferent impulses to the medullary vomiting center, which in turn initiates emesis (9, 10). Droperidol is a neuroleptic butyrophenone used clinically for sedation and antiemesis. The drug inhibits dopamine receptors in the trigger zone and thus acts centrally to decrease nausea. Although droperidol is a potent antiemetic, it may produce side effects that must be monitored. As a dopamine receptor inhibitor, it may produce extrapyramidal signs. It is also an alpha adrenergic antagonist, and hypotension is a possibility. Other side effects include anxiety and drowsiness. In this study we saw no instances of droperidol-related side effects. One patient did feel subjectively lethargic enough to request discontinuation of the PCA pump, even though he appeared awake and alert throughout.

Although sedation scores were slightly higher in the droperidol group, the difference was not statistically significant. The amount of droperidol used in that group was 3.8 mg over 44 hours, an average rate of 0.09 mg/hour. A usual antiemetic dose of intravenous droperidol is 0.625 mg–1.250 mg and the half-life is 4–6 hours; the cumulative amount of droperidol received by patients in this study was therefore clinically acceptable for the treatment of nausea.

The median pain scores were similar in the two groups. The study group needed 42% less morphine sulfate than the control group to maintain this similar rating. Droperidol has been shown to bind to opiate receptors. Structurally,

butyrophenones are similar to opioids, and pharmacological studies have demonstrated a weak opiate agonist action for droperidol (11). This might explain how the morphine sulfate plus droperidol system decreased the amount of morphine sulfate needed to produce adequate analgesia, although further studies are needed to definitively delineate the mechanism. Recent studies evaluating the addition in PCA of droperidol to morphine sulfate have not found this morphine-sparing effect, but these studies differed from the present study in shorter study durations (12, 13); the absence of control groups (14, 15); differences in patient populations (12, 14, 15); and smaller droperidol concentrations (12, 14).

In our study population, no opioid side effects (itching, respiratory depression) other than nausea and vomiting were noted. In a larger study group one might expect a decrease in opioid side effects associated with the smaller doses of morphine sulfate used.

In conclusion: the results of this study show that the addition of droperidol to a morphine sulfate PCA system used for the treatment of postoperative pain in patients who have undergone orthopedic procedures on an extremity decreases the incidence of nausea and vomiting without incurring significant droperidol-related side effects. The addition of droperidol also achieves adequate pain control with less morphine sulfate. Further studies will be necessary to determine if this system is practical for patients who require larger doses of morphine (because they are opiate tolerant, for example).

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A Harvard Medical Student Chronicles His Fatal Illness:

The Story of Alfred S. Reinhart, 1907–1931

BURTON I. KORELITZ, M.D.

I, A GASTROENTEROLOGIST, am presenting the story of Alfred Reinhart, who lived with and died at age 24 of a cardiac disease, for reasons I explain at the end of this paper. I start with an introduction to a commemorative issue in honor of Solomon Berson, M.D., Director of Medicine at Mount Sinai Medical Center, who died in 1972 (1), written by my dear friend, the late Dorothy Krieger: "It must have been as a medical student that Sol read an article in *The Journal of the Mount Sinai Hospital* that he was particularly fond of quoting on medical student rounds. This was by Soma Weiss on some observations of 'medical student A.S.R.,' who described his own case of subacute bacterial endocarditis" (2).

As a medical student in Boston, I too had read and been touched by these observations about the short life of this brilliant medical student who, just a few years later, might have been saved by sulfonamides and penicillin. When I arrived at The Mount Sinai Hospital as an intern in 1951, I met Joseph Globus, then editor of *The Journal of The Mount Sinai Hospital*. He showed me an original issue of a 1942 *Journal* festschrift, a memorial to B. S. Oppenheimer, which contained a chronicle of disease dictated by the patient and medical student, Alfred S. Reinhart (Figs. 1, 2), in an article submitted by Soma Weiss, Professor of Medicine at Harvard Medical School and the Peter Bent Brigham Hospital, who was Reinhart's preceptor (2) (Fig. 3).

Weiss wrote in his introduction "much has been written on the bacteriological and immuno-

logic aspects and on the post mortem findings in Subacute Bacterial Endocarditis, but the symptoms have received surprisingly little consideration. It is indeed a rare opportunity in any disease to obtain an intelligent and complete story with subjective sensations well related to objective findings. Alfred S. Reinhart was a fourth-year student in the Harvard Medical School and a young man of exceptional ability. It is hoped that physicians may read with profit this record of his keen self-observations with its philosophical remarks, written during the course of a disease which he recognized as hopeless."

Summary of A.S.R.'s Medical Case

History. A.S.R. (Adm. 29669) was admitted to the Peter Bent Brigham Hospital on June 17, 1921, at the age of 13 with chorea two months after a diagnosis of rheumatic fever was made.

There was a blowing systolic murmur over the apex, a swelling of the second joint of the fourth finger of one hand and blood pressure of 120/0. On July 19 he was free of choreiform movements, a distant aortic diastolic murmur was heard over the apex and a blowing diastolic over the base. On August 3, the x-ray indicated a moderate degree of enlargement of the heart. The temperature and heart rate were elevated during the first week, but subsequently returned to normal. He was discharged on August 16, 1921.

Second Admission. Ten years later, the patient (Adm. 74933) was readmitted to the Peter Bent Brigham Hospital, on July 23, 1931. In the spring of 1931, following measurement of his blood pressure, he noted a small circle of subcutaneous red spots which did not fade on pressure.

Adapted from a presentation at Lenox Hill Hospital on June 3, 1993. Address reprint requests to the author, Chief, Section of Gastroenterology, Department of Medicine, Lenox Hill Hospital, 100 East 77th Street, New York, NY 10021-1883.

The patient suspected subacute bacterial endocarditis. A short time afterward, when he had run across a street, he developed showers of premature beats which lasted for ten days.

On examination, there was marked visible pulsation of the carotid arteries with a thrill and a loud systolic murmur. The apex impulse was 13 cm from the midline in the sixth space. There was a loud systolic and a high pitched diastolic murmur over the aortic area. The pulses were Corrigan in type. Pistol shots were heard over the brachial and femoral arteries, but Duroziez's sign was absent. The blood pressure was 140/0. No petechiae were seen. Rheumatic fever with heart disease and with aortic insufficiency was diagnosed. On August 2 a positive blood culture for *Streptococcus viridans* was obtained, and thus the diagnosis of subacute bacterial endocarditis became established. Various methods of treatment were tried without benefit. On August 24, he developed left upper quadrant pain.

On September 11, the patient was transferred to the Thorndyke Memorial Wing of Boston City Hospital, where the findings were as described above. His temperature varied from 100° to 101°F. The spleen was palpable. On September 14, 1931, tenderness and slight swelling of the right index finger developed, with a vaguely circumscribed red spot. The white cell count of the blood was 12,000 to 16,000 per cm. By September 18, numerous petechiae had appeared. The spleen became larger. On September 25 he developed an attack of acute pain under the left costal margin which became worse on inspiration. Extreme tenderness was experienced over the spleen. During the next two weeks various embolic manifesta-

tions, sore muscles and joints, and tender cutaneous nodules developed. Beginning October 18, the patient developed transient attacks of aphasia, and on October 21 complete right hemiplegia occurred. On October 26 he developed pulmonary edema and died.

Autopsy. The leaflets of the aortic valve were thickened and retracted, and slight fusion existed at the juncture of the cusps. There were numerous soft vegetations attached to the aortic cusps. The large ones projected into the lumen of the opening of the valves, growing mainly over the cardiac surface of the cusps. The vegetations continued downward toward or onto the aortic leaflet of the mitral valve.

Anatomic Diagnoses. Subacute bacterial endocarditis (aortic and mitral); old rheumatic endocarditis with aortic insufficiency; infarctions of the spleen, kidney and brain. Culture of the blood obtained from one of the cardiac chambers yielded *Streptococcus viridans*.

A.S.R.'s Chronicle

I have collected choice quotations of Alfred Reinhart from Weiss's article and from Weiss's original unpublished notes, which were supplied to me by Richard Wolfe, curator of the Francis A. Countway Library of Medicine in Boston. Reinhart's remarks are interspersed with comments of my own obtained from a variety of sources.

Reinhart wrote of the start of his chronicle:

Dr. Weiss has generously loaned me the services of a Hospital Secretary for several minutes every day. It is my plan to spend these minutes on the evolution of a generally fatal disease, and my design is to constitute observations on its



Fig. 1. Alfred S. Reinhart at age 14, after his rheumatic fever and first hospitalization.



Fig. 2. Alfred S. Reinhart at age 21 in 1928. Reprinted with permission from Yearbook of Harvard College, p. 242.



Fig. 3. Soma Weiss.

natural history and course including memoirs of the subjective reactions of a patient to that disease. The pathogenesis of a disease must be sought usually in the records or reactions long antedating the immediate symptomatology. In this regard, I must look for the genesis of the present disease at least ten years back to the time I was afflicted with chorea and rheumatic fever with resulting damage supposedly only to the aortic valve. The fact that the only or principal lesion was aortic is, of course, of significance in the understanding of later events. Aortic regurgitation, as is well known, carries with it a syndrome of hemodynamic phenomena, which are among the most striking in the entire field of physical diagnosis.

For ten years now, I have carried a blood pressure ranging on the average of 160 systolic and 0 diastolic, a fact, which translated into physical emotions means, especially when we consider the existence of the *cor bovinum* of aortic insufficiency, that every ventricular systole is sensed by the patient with no effort on his part. The physical discomfort of being forced to experience every ventricular systole over a long period of years is not to be underestimated, and I had often felt willing to sacrifice many things in order to feel again how it was to be able to live without feeling my heart beat. With this physical and psychological handicap, I was able to complete perhaps with a better than the average degree of success, school, college, and three-fourths of medical school.

Who was Alfred Reinhart? His parents emigrated from Eastern Europe in the late nineteenth century and settled in Boston, where all three of their children were born, the oldest in

1898 and Alfred, the youngest, in 1907. The family was Jewish. Reinhart graduated from grammar school at 11, after receiving several double promotions. He was bar mitzvahed at 13. That year he developed St. Vitus dance, and his family doctor warned that he might not live overnight. He was admitted to Peter Bent Brigham Hospital, where he could not be held down; he was treated with ice-cold showers. This presumably was the onset of his rheumatic fever. He lost a year of school because of illness, but his mind did not stop working, and he read and absorbed information on many topics during that period (Fig. 1). He entered English High School, where he continued to excel. He remained well but not robust for the next five years. He was admitted to Harvard College in 1924 at age 17 and majored in Government and English. His main interests were law and writing. He was appointed an assistant literary editor of the *Boston Transcript* and supported himself during his college years by writing reviews of books. As he approached graduation, influenced by his own illness and impressed with how little was known about it, he decided that he wanted to help others. He switched his major and applied for medical school.

He graduated from Harvard College in 1928, where he had achieved Dean's list and Phi Beta

Kappa (Fig. 2). Later that year, he entered Harvard Medical School, and until early in 1931, received many scholarships and also “moonlighted” as a subintern. He made house calls on “charity” patients and even found time to spend a few hours in the laboratory doing research. It was during medical school that he wrote his paper on the origins of rheumatic fever (3), which was accepted for publication by the *New England Journal of Medicine*. During his three years of medical school he acquired the medical acumen to understand his own case:

There began to shape themselves in my mind three fears relative to my ultimate fate, which albeit, I had not usually looked before as being very near. I know there were always three octopi ready to grab me in their tentacles at the first feasible opportunity: (1) a recurrence of Rheumatic Fever, (2) cardiac decompensation, for I was leading a very active life, and (3) subacute bacterial endocarditis.

The first consideration of subacute bacterial endocarditis entered his mind in January 1931, out of his knowledge that it was possible and his subjective feeling of fullness in the right upper quadrant, particularly when taking a hot bath. He also noted early clubbing of his fingers. Thereupon, he recounts, “I thought the wisest policy would be to consult those who knew more about medicine than I did, and I referred to the office of Dr. A who found no signs of subacute bacterial endocarditis.” I subsequently learned from the unpublished notes of Soma Weiss that “Dr. A” was Samuel Levine, the famous cardiologist.

Reinhart did well until May 1931, when, while running across the street to avoid an oncoming automobile, he experienced a

procession of extrasystoles unprecedented in their frequency. The condition grew worse, study and even sleep became impossible and life itself was almost intolerable. I was trying to study medicine and each known fact literally seemed to be hammered into my head by a cannon. The only relief that I could devise was getting up at night and walking around, thus increasing the heart rate.

With two of my National Board examinations yet to be taken, at approximately quarter to twelve, I remember distinctly getting up from my chair, removing the left arm of my suit coat, and there on the ventral aspect of my left wrist was a sight which I shall never forget until I die—fifteen or twenty bright red, slightly raised hemorrhagic spots about one millimeter in diameter which did not fade on pressure and which stood defiant, as if they were challenging the very gods of Olympus. There was no mistaking the sign; it had only to be read. I calmly said to my sister-in-law, who was standing nearby: I shall be dead within six months.

Reinhart called Levine, whom he knew personally, but Levine was out of town at a convention. He then called “Dr. B,” who, from the notes

of Weiss, I learned was Herrman Blumgart, Director of Medicine at the Beth Israel Hospital, another of Reinhart’s preceptors. Blumgart, like Levine, was at the out-of-town convention. Eventually Reinhart regained his composure and tried to sleep.

In the morning the spots were not so red. Their disappearance and the lack of their reappearance proved to be a little embarrassing in later weeks when discussing their significance with fellow students and house officers. “This must impress the medical clinician of the difficulty of eliciting accurate histories from even the most intelligent of patients.”

Reinhart would see red streaks on his fingers come and go. He then had blood cultures and skin tests. The skin tests were all highly positive except for the *Streptococcus viridans* (the organism associated with subacute bacterial endocarditis), which was considered neutral. Since fully positive tests were considered to signify “immunity,” the results were regarded as favorable and as virtually excluding subacute bacterial endocarditis. But—as clinicians later learned—this was just another instance in which the laboratory was not king.

Reinhart was at that time scheduled to start fourth-year surgery at Massachusetts General Hospital, and he also had an appointment with Soma Weiss, who he was going to assist as a tutor. Personal documents indicate that because of the pressures of his circumstances, he postponed both. He borrowed \$100 from his brother-in-law and took a trip to New York that lasted almost two weeks. Weiss’s article quotes A.S.R. as saying:

I gained several pounds in weight despite the fact that I was very active during the entire time, and secondly I met a young lady with whom I became quite familiar and whose sister had died three or four weeks previously of subacute bacterial endocarditis, a fact which I did not learn for some days after meeting the girl, and a fact which did very little to calm my uneasy mind. During the same time, I learned of the death of a school classmate of mine from subacute bacterial endocarditis and I spend some time listening to the details of the horrors of the mode of exodus.

Reinhart reported in his personal documents: “despite this I think I never spent any two such enjoyable weeks in all my life as I spent in New York, and returned to Boston feeling a much fuller man from the sights I had seen, the places I had visited, the people I had met.” In Weiss’s original notes, he quotes A.S.R. as saying: “On Wednesday, with the kindness of the Surgical Resident of the Y Hospital [Massachusetts General Hospital] and with the courtesy of his staff, I began my Fourth Year course and enjoyed it.”

At the end of the second week in the surgery course, he noted soreness in the back of his knee, which he attributed to standing in the operating room. While walking up the hill from Cambridge Street to Bowdoin Square he noted soreness in his right leg and he started to limp. He had left the hospital at 7:00 PM, unusually early for him, and was barely able to reach his home. The soreness intensified during the evening. His family doctor was called and made a diagnosis of rheumatic fever, but Reinhart observed that his knee was not red, swollen or hot. Nevertheless, Reinhart accepted heavy doses of aspirin and oil of wintergreen packs; they were not helpful. After a week, Dr. Levine came to see him at home; he too made a diagnosis of rheumatic fever and advised immediate admission to the Peter Bent Brigham Hospital. Reinhart expressed his fear of subacute bacterial endocarditis but Samuel Levine reassured him.

When asked by the admitting house officer and resident what his chief complaint was, he told them subacute bacterial endocarditis. They thought very little of this chief complaint and assigned the diagnosis of rheumatic fever. In due course, when heavy salicylate therapy was not effective, the possibility of infectious arthritis was considered. One blood culture was negative, as were other laboratory tests.

While the diagnosis of infectious arthritis was under consideration, a second blood culture was taken, and my fate was sealed. The green producing streptococcus was found on the culture medium, and the diagnosis which I stoutly defended for more than a month, against the protests of all those around me, now was unfortunately confirmed . . . here was the last link in the chain. I had previously had inculcated into me the fact that I was going to die within a comparatively short period of time, but I could always find a leeway out. I could always find a loophole in the evidence here and there however untenable I knew these loopholes to be, but now I was confronted with the *dictum ultimum* from which there was no escape. I do not exactly recall my reaction to this message from the Angel of Death, although as I remember it, I showed no emotional change whatsoever.

At this point the thought occurred to him (according to his personal notes) to go to the Rockefeller Institute as a patient for experimental investigation.

What Reinhart's total plan was in coming to New York is not clear. The apparent attraction to Rockefeller Institute was a "Dr. E" (Homer Swift), who Reinhart knew from the medical literature was interested in rheumatic fever and in vaccines against streptococci. Articles in Boston newspapers published in 1931 state that he came to New York seeking Emanuel Libman, who, so

the article states, was associated with Rockefeller Institute. Apparently there was some miscommunication, because Libman's association with The Mount Sinai Hospital was well known. A member of Reinhart's family remembered that it was Libman he wanted to see while he was in New York. Unfortunately, Libman had just left for Europe.

Coincidentally, I learned in a personal communication from one of Reinhart's classmates, Dr. Edward Budnitz, that Libman had spoken at Medical Grand Rounds at the Peter Bent Brigham Hospital during the time of Reinhart's second hospitalization on the subject of subacute bacterial endocarditis. Unfortunately a visit to Reinhart could not be arranged.

Reinhart wrote at some length about the various therapeutic options that were then available, noting that it was logical that they would fail:

By this time I was quite reconciled to my fate, but nevertheless was continuously seeking new treatment. I am entirely sincere when I say that I sought new treatments not in any serious endeavor to cure the disease or prolong my life, but simply to satisfy the urge that something be done.

Reinhart provided a vivid description of two episodes of splenic infarctions:

One of the most dramatic episodes in clinical medicine is the splenic infarct which occurs in malignant endocarditis. In its histrionic appeal, it must be classed with coronary thrombosis, acute mesenteric occlusion and postoperative pulmonary embolism. However, at least from the basis of my own experience, I am forced to wonder whether the splenic infarct is exactly what the older clinicians, such as Osler and Janeway, have described it to be. These gentlemen describe the splenic infarct as occurring with indescribable suddenness and accompanied by intolerable pain. If I remember correctly, Osler remarks that an embolus to the spleen may be the first warning and the only sign of a deep-rooted ulcerative endocarditis. It is certain, its existence would always be considered by surgeons in making a differential diagnosis of the so-called acute abdomen.

He went on to characterize his own experience, particularly the effect of position and motion and the drinking of fluids, on the intensity of the pain (no less than that endured by women during delivery), and the use of morphine and scopolamine:

At approximately midnight I noticed that it was slightly uncomfortable for me to lie on my left side without any localization. One or two hours later it became uncomfortable to be on my back, at three o'clock I was generally uncomfortable and at four o'clock I was sitting up in bed in distress. The nurse wanted to call the house officer, but I asked her not to. At five o'clock the pain in the left upper quadrant became intolerable and I requested assistance.

In Reinhart's original notes he goes on to say,

Every so often in our daily social contacts, we are overtaken by some remark or deed which we cannot fathom or under-

stand. It was just such a statement which greeted my ears at this time. Whether through sheer indiscretion or through some personal factor, which I didn't understand, the night nurse informed me that the doctor's reply to my request for assistance was:—"Tell Mr. Reinhart that, if he is going to get embolic phenomena, to get them at a more earthly hour." [The house officer did later come and apologize.]

In conclusion I do not wish to leave the simple impression that splenic infarct does not occur with great suddenness. I simply think that it is nearer the truth to say that maximum intensity of pain is reached in a comparatively short time as opposed to its instantaneous occurrence. Undoubtedly there might be much more said about the role of the spleen in subacute bacterial endocarditis, but I think I shall have to leave the subject of the spleen here and in a subsequent note go on to another topic. Indeed, one is reminded of the story of the German Professor of Physiology who said: "Gentlemen: we come now to the story of the spleen. We know nothing of the spleen, so much for the spleen. We will now take up the liver."

Reinhart concludes his own presentation by discussing extrasystoles:

It [the extrasystole] has always affected me as if a cannonball [were] shot point blank at my brain, like a terrific explosion occurring within the narrow and limited confines of a calcified skull which refuses to yield to the compressing force. I had even at times attempted the very dangerous exploit of exerting double vagal pressure against all the advice of famous clinicians but this pressure neither killed me nor stopped my attack of paroxysmal tachycardia.

Only a deep inspiration would help, but the pain of the splenic infarcts was markedly accentuated by the inspiration. He solved it by forced expiration, and wrote: "I have freed myself from God knows what, merely by breathing out the last drop of breath that was in me."

Reinhart had related every symptom of his illness until two days before his death on October 26, 1931.

Weiss provided some final comments on Reinhart's various emotional states and reactions as the disease progressed. But perhaps Weiss's most poignant remarks on Reinhart's life are in Weiss's introduction, in the section I have already quoted at the beginning of this article, where he speaks of the "rare opportunity" that Alfred S. Reinhart's chronicle affords: "to obtain an intelligent and complete story in which the subjective sensations [of a disease] are well related to objective findings."

Reinhart's mother received a telegram from the superintendent of the hospital after Alfred's death, and classes at Harvard Medical School were canceled on the day of the funeral. Mayor James Curley wrote a letter published in the *Boston Herald* along with Alfred's history, his picture, and a picture of his mother. Editorials ap-

peared across the country, including one in *The New York Times*. Condolences arrived from friends, classmates, teachers, and strangers who had read about this case. Soma Weiss wrote, "After his death, I went over his notes with particular care and was more impressed than ever by his keen observations and ability." Samuel Levine wrote, "I would be proud to have a son of his sort and his purpose in life."

In 1992, at the 60th reunion of Reinhart's Harvard Medical School class, a classmate noted (4): "In the spring of 1932, Harvard Medical School sent out into the world 120 ambitious starry-eyed fledgling doctors. We should not forget the bright young classmate, who shall always remain young Alfred Seymour Reinhart who tragically passed away during our fourth year of a disease he would now survive." (The classmate was Seebert Goldowsky.)

A.S.R.'s Personal Legacy

From his deathbed at Thorndike Memorial, Reinhart wrote this letter to his nephew:

Jason my Love—

To you I leave my watch, which Grandpa gave me, and my Phi Beta Kappa key, which you will keep as a life-long remembrance. I leave you also my library in your house now.

I hope you will live long and keep well, that you will go through school and college and try by all means to go to Medical School. If you can go to Harvard, my record may possibly do you some good, although in your time there will probably be few to remember me. Remember your Parents and your health above all other things. Obey, honor, love, respect your father and mother and you will be honored and respected by all.

Do not forget by any means to get at least one or two good vacations a year. This is especially true as you grow older and older. Be also devoted and loving and respectful to your parents' other children. Be kind to people and be truthful and honest at all times.

As the first of my nephews I love you as I could love few people and I hope you will live in a way to merit my hopes for you.

Uncle Alfred

Reinhart hoped that his sister, whose third child was soon to be born, would name a son after him, but his sister delivered a daughter, Madeline, so there was no relative named "Alfred." Later in life Reinhart's niece wrote: "As I groped my unsteady way into the world I was quite unaware of the valiant courageous life which was being snuffed out—just 10 days after I was born."

Alfred's mother was Lena Reinhart. She lost both her husband and her son in the same year and came to live with her daughter, Ada, in Lawrence, Massachusetts. That daughter was my mother, Ada Reinhart Korelitz, born in 1900 and still alive and well. Jason, who received the

deathbed legacy, was my older brother. He devoted his professional life to journalism. I was the second son, five years old at the time of my uncle's death, and A.S.R.'s legacy was not intended for me. But I received it nonetheless and took it deeply to heart—a passionate desire to become a physician, a profession which has provided me with profound fulfillment and endless satisfaction.

A.S.R.'s Legacy to Medicine

I believe that there are other messages which can be gained from Reinhart's story:

- Despite the loss of respect for the medical profession, fear of less lucrative financial returns in the national health program, and loss of initiative for clinical and research achievement, I suspect that had Alfred Reinhart survived subacute bacterial endocarditis, he would have overcome all of these obstacles and continued to make many meaningful contributions.
- There will always be a solid core of physicians who, like Reinhart, will seek and achieve the highest. It is my own conviction that the potential for a career in medicine is perhaps more exciting now than ever.
- Although medical technology has made tremendous strides in the last 60 years, the clinical value of careful observations and documen-

tation should never be underestimated or compromised in the sequence of events leading to precise diagnosis and management. The sense of satisfaction and achievement attained by the managing physician is exalting when the observations derived from the patient's history and physical examination are fully integrated with results provided by advanced technology.

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A.S.R. and Medicine

KORELITZ'S PAPER "A Harvard medical student chronicles his fatal illness: the story of Alfred S. Reinhart, 1907–1931" provides the opportunity to think about the teaching and practice of medicine. The original paper, which appeared in the *Journal* more than half a century ago, addresses the highest values of the profession. The medical student, the patient, is a scholar par excellence and a keen observer. His professor recognizes these talents and provides the student with secretarial time to facilitate recording whatever the student might dictate about his own illness. Would the professor have made the time to listen to a tape recording? I doubt it. However, he reads the written record of what has been said, is awed, and preserves it. Weiss has the wisdom to retain the patient's criticism of physicians' behavior, which is done in such an elegant way. He submits the material for publication, albeit some ten years later. And now teachers like Berson and students like us all can benefit from the work done in the days of and by the giants.

Yes, progress in medicine has provided dramatic changes in therapy for this disease. Has this progress eliminated the art of listening to the patient and examining the patient? Certainly not! Perhaps this progress demands that we redouble our resolve to listen to and appreciate what is being said and presented by the patient. Our choices on how to proceed, with what technology and what therapy, can be channeled most effectively only after that successful interactive encounter. This is the lesson that Weiss and Berson, and many others, learned from this patient and student and must have taught their students.

Korelitz mentions having met Globus in 1951. Globus was well aware of the roles of Emanuel Libman and George Baehr at The Mount Sinai Hospital with respect to their contributions to the literature on subacute bacterial endocarditis.

Emanuel Libman came to Mount Sinai in 1896 as a house officer. He was an outstanding

clinician, ultimately serving at The Mount Sinai Hospital as chief of the First Medical Service and associate director of the Laboratories. He was recognized, along with William Osler and Thomas Horder, as one of the world's foremost authorities on subacute bacterial endocarditis (1). Osler had described the disease as malignant endocarditis (2, 3) and Horder had referred to it as ulcerative and infective endocarditis (4, 5). William H. Welch of Johns Hopkins considered Libman to be this "country's outstanding authority on the disease" (6). Welch remarked that Libman's reports included "every aspect of the disease—bacteriological, etiological, pathological, clinical and preventive" and that they "doubtless represent the high-water mark of his research activities and furnish a good example of his command of technique and of his powers of keen observation, critical analysis, and sound inference. Libman and his co-workers' studies . . . embrace all forms of cardiac disease and abnormality. . . . So numerous, original, comprehensive and important have been the studies of the heart emanating from the wards and laboratories of Mount Sinai Hospital that I think one can correctly speak of the Mount Sinai school of cardiologists, of which Libman was the founder and guiding spirit" (6).

Libman already had established the value of the blood culture in general clinical practice (7, 8). In February 1911, he was called in consultation to see Gustav Mahler, the famous composer and then conductor of the New York Philharmonic Orchestra (1) in the latter's hotel room. After Libman's examination, which unequivocally supported the clinical diagnosis of subacute bacterial endocarditis, he telephoned George Baehr, his student and assistant, to come to the hotel with the equipment and media needed for the blood culture (9). The recovery of streptococci, ultimately identified as *Streptococcus viridans*, from the blood cultured in their laboratory confirmed the diagnosis. Mahler returned to Vienna and died in May at age 51. We have come to learn

that the course of the disease in both Reinhart and Mahler was very similar.

Libman is credited with describing the disease and calling it subacute bacterial endocarditis, as we now do. Baehr went on to describe in great detail the glomerular lesions, reported earlier by Löhlein (10), which had been found in the many cases of subacute bacterial endocarditis that both he and Libman had seen (11).

It is entirely fitting and appropriate that the Journal acknowledge the contributions made by those who have been held in high esteem by recalling their names and deeds. While great strides have been made in understanding the pathophysiology of many diseases and in the effectiveness of their treatments, much is yet to be done. The clarity and style offered in these classic papers remain to be emulated as a tribute to their timeless virtue.

SHERMAN KUPFER, M.D.
Editor-in-Chief

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Transvaginal Small-Bowel Evisceration:

A Case Report

DENISE ROLLINSON, M.D., MICHAEL L. BRODMAN, M.D., FREDERICK FRIEDMAN JR., M.D., AND
RHODA SPERLING, M.D.

Abstract

Transvaginal small-bowel evisceration is rare. Only 47 case reports appear in the literature in English. Review of this literature shows that vaginal evisceration occurs mainly in women who are older, multiparous, and have undergone vaginal surgery. The immediate cause of evisceration is either sudden, increased intraabdominal pressure, trauma, or a spontaneous event. The small bowel and omentum are most commonly involved. Surgical repair is performed vaginally, abdominally, or by both methods. We present a case of transvaginal small bowel evisceration caused by inadvertent self-induced trauma, a heretofore unreported cause of this complication, in a 79-year-old woman with known weakness of her pelvic structural support. She experienced sudden evisceration of small bowel following manual decompression of her cystocele during voiding. We used a combined abdominal and vaginal approach to examine the small and large intestines and mesentery for trauma, attach the vaginal vault to the shortened uterosacral ligament, obliterate the cul-de-sac using the Moschowitz procedure, and repair the defect in the levator plate.

To limit risk, patients should be evaluated for predisposing conditions. We recommend a combined abdominal and vaginal surgical approach to adequately evaluate the involved tissues and to effect repair.

VAGINAL EVISCERATION is extremely rare. In 1990, Guttman and Afilalo reported a total of 50 cases in the world literature, including one of their own (1). Vaginal evisceration occurs mainly in postmenopausal women who have atrophied, devascularized vaginal membranes and connective tissue, due to the lack of estrogen, and weakened pelvic support structures resulting from childbirth, hysterectomy, radiation, or carcinoma (1-7). Immediate precipitating factors of evisceration in older women include increased intra-abdominal pressure and trauma; in younger

women, precipitating events are more likely to be coitus, traumatic childbirth, and foreign bodies (1-5). We report a case of transvaginal small-bowel evisceration caused by inadvertent self-induced trauma in a 79-year-old woman with known pelvic structural support weakness.

Case Report

A 79-year-old white woman, gravida 2, para 2, was seen in October, 1992 with a chief complaint that something had "fallen down" from her vagina. Twelve years prior to admission, she underwent an uncomplicated vaginal hysterectomy for uterine prolapse. Three years prior to admission, she was diagnosed with recurrent vaginal vault prolapse and a cystocele. Medical management, including the use of a pessary, was ineffective. The patient experienced progressive difficulty defecating and voiding; manual decompression of the bladder became necessary in order to urinate adequately.

Three weeks prior to admission, gynecologic

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From the Department of Obstetrics, Gynecology and Reproductive Science, The Mount Sinai School of Medicine, New York, NY. Address reprint requests to Michael L. Brodman, M.D., Department of Obstetrics, Gynecology and Reproductive Science, The Mount Sinai School of Medicine, 1176 Fifth Avenue, Box 1170, New York, NY 10029.

evaluation confirmed the presence of vaginal prolapse and total eversion of the vaginal vault, with protrusion of the bladder and rectum; the mucosa was intact. Vaginal estrogen cream was prescribed and surgical repair was scheduled.

Three days prior to the scheduled operation, during preadmission testing at the hospital, the patient manually reduced her cystocele to provide a urine specimen. She experienced sudden intense pelvic pain, associated with a sensation of "something falling down" from her vagina, and called for help.

The patient was appropriate weight for height, and had no history of obesity or obstructive pulmonary disease. Her medical and surgical history were otherwise noncontributory. Her obstetric history was significant for two uncomplicated spontaneous vaginal deliveries. Additional gynecologic history was significant for natural menopause 30 years before without postmenopausal hormone replacement. Routine cytologic evaluations were normal.

Gynecologic examination revealed transvaginal evisceration of approximately three feet of small bowel. The bowel was pink, slightly edematous, but well perfused, with waves of peristalsis, and no evidence of infarction. Saline soaks were immediately applied to the eviscerated bowel.

The patient underwent an emergency exploratory laparotomy with broad-spectrum antibiotic coverage. The eviscerated bowel consisted of three feet of ileum, up to approximately 10 cm from the ileocecal valve. The bowel appeared viable and was reduced back into the abdomen. A modified Moschowitz procedure was performed along with a posterior colporrhaphy to correct the defect in the levator plate. The patient tolerated the procedure well.

On postoperative day 8, a ventilation-perfusion scan demonstrated a small pulmonary embolism in the right upper lobe. Anticoagulation therapy was initiated; the patient was discharged on hospital day 15.

Discussion

Reviews of vaginal evisceration have been published by a number of authors (1-5). Associated factors include older age, parity, and previous vaginal operations. Evisceration is often precipitated by sudden increased intra-abdominal pressure or trauma. The surgical repair may be abdominal, vaginal, or both. We reviewed and analyzed the English-language literature on vaginal evisceration, which consisted of 47 reported cases (1-17).

The patient's age was given in 40 of the cases. The mean age of the patients was 60.4 ± 15.4 years. Twenty-nine (72.5%) of these patients were 50 years old or more. The patient's parity was given in 30 of the 47 cases; the range was from 0 to 10 (mean 3.5 ± 2.8). In 43 cases in which a history of previous vaginal surgery was given, the number of previous operations ranged from 0 to 4 (mean 1.3 ± 1.4). The interval from the last operation to time of evisceration was known in 33 of the 47 cases; the range was from 2 months to 30 years (mean: 39.5 ± 69 months). The site of rupture was known in all but one instance. The evisceration occurred at the posterior fornix in 19 cases (41%), the site of enterocele in 13 reports (28%), the vaginal vault in 6 cases (13%), the apex of the vagina, the vaginal cuff, or the site of a previous operation in 6 cases (13% total), the left lower uterine segment and vaginal fornix in one case, and at the site of an enterovaginal fistula in one case.

The immediate cause of evisceration was known in 33 of the 47 cases (70%). Of these, 14 cases (42%) were precipitated by sudden increased intra-abdominal pressure (by Valsalva maneuver, coughing, vomiting), 13 cases (40%) were due to trauma (coitus, traumatic delivery and instrumentation, foreign body), and 6 cases (18%) were precipitated by nontraumatic events (standing in line, walking). The viscera most commonly involved were the small bowel (41 cases; 87%) and the omentum (4 cases; 8%); less commonly involved were the appendix epiploica and the pelvic colon (one case each). Protrusion of small bowel from the introitus was reported in only 11 patients (23%).

The surgical management of evisceration was described in 43 of the 47 cases. Repair was performed either vaginally (16 cases, 37%), abdominally (15 cases, 35%), or by combined approach (12 cases, 28%).

Vaginal evisceration primarily occurs in postmenopausal women for many reasons. Postmenopausal women often have atrophied pelvic support structures, thinner vaginal membranes, and foreshortened vaginas with decreased vascularity (1-5). Stresses superimposed on the already weakened pelvic supports include previous vaginal surgery, altering the stress point on the levator plate; presence of an enterocele (which demonstrates an existing defect in the pelvic supports); increased intra-abdominal pressure; radiation therapy; and carcinoma (3-7, 10, 19, 20).

Parity and previous vaginal surgery are thought to contribute additional stress to the pel-

vic support structures. Childbirth injuries tend to stress the weaker, sacral part of the uterosacral ligaments, and hysterectomy removes the stronger, uterine part of the uterosacral ligaments (18). Because the reported average parity and number of previous vaginal operations were both low, the number of deliveries or surgeries is not necessarily implicated; rather it is the degree of obstetric or surgical trauma inflicted on pelvic support structures that is associated with vaginal evisceration (19).

In the patient reported on here, the interval from last operation to time of evisceration was 12 years, a period consistent with other cases in the literature. The site of rupture was the vaginal cuff, presumably due to self-inflicted trauma superimposed on weakened pelvic support structures and thinned vaginal membranes and connective tissue. The viscera involved in this patient's case was the small bowel, which is the viscera most frequently involved in reported cases. However, despite a large amount of bowel protruding from the introitus, the viability of the bowel was preserved. This case is unique in that the immediate cause of evisceration was self-induced trauma as the patient attempted to manually reduce her cystocele in order to void for a urine specimen.

The emergency management of vaginal evisceration is critical to the preservation of bowel viability. Guttman and Afilalo emphasized the following five points in the emergency care of a patient with bowel evisceration: (a) stabilizing the patient; (b) managing the patient's fluid status; (c) preserving the bowel with moist saline sponges; (d) early antibiotic treatment covering gastrointestinal flora; and (e) immediate surgical repair (1). The fact that this patient's evisceration occurred at the hospital facilitated immediate action on each of these procedures; this allowed complete preservation of bowel.

Complications of transvaginal evisceration include ileus, infection, and wound disruption. There is a reported 10% mortality rate, usually due to thromboembolic complications (10). This patient developed a small pulmonary embolism postoperatively, but recovered without complications.

The surgical repair performed on this patient is unique for patients with grossly eviscerated bowels in that we elected to utilize both an abdominal and a vaginal approach. Our decision-making process was influenced by two facts: the patient had a traction enterocele type vault inversion, as described by Nichols (20), and we were unable to determine if the prolapsed small bowel

had caused trauma to the mesentery, which was concealed intra-abdominally. An exploratory laparotomy was clearly needed to adequately evaluate the remaining large and small intestines.

A large defect in the levator plate with a traction enterocele and cystocele is best repaired transvaginally (19, 20). The approach we propose follows the Nichols model (19, 20). Patients with no vault prolapse who have an evisceration through a posterior enterocele can be repaired vaginally if there is no bowel protrusion through the defect. The abdominal approach must be performed if the bowel needs to be examined. It can also be selected if the surgeon prefers a Moschowitz or Halban repair (19, 20).

In cases of pulsion or traction enterocele with bowel evisceration, we recommend the combined abdominal-vaginal approach to (a) inspect the length of the intestines for damage; (b) attach the vaginal vault to the shortened uterosacral ligaments; (c) obliterate the cul-de-sac using the Moschowitz procedure; (d) repair the defect in the levator plate with a posterior colporrhaphy. Following these steps, one repairs all of the defects in the pelvic floor.

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Neurologic History of George Gershwin

ALLEN SILVERSTEIN, M.D.

GEORGE GERSHWIN was not only a superb composer of popular music and to a lesser extent of classical music, but he also was a gifted pianist and a talented conductor. The music he played or conducted was usually written by him, and despite his short life, was enough to fill a formal concert performance or to satisfy the many informal parties at which he loved to play the piano. Gershwin wrote the music for over 550 popular songs, which appeared in 44 Broadway shows, 49 Hollywood films, and 2 operas; and he also wrote several classical pieces.

He died of a glioblastoma of the right temporal lobe at the age of 38 on July 11, 1937.

Three articles have already appeared in the medical literature about his death (1–3). The purpose of this communication is to review the neurologic history of Gershwin's fatal illness, and to discuss further what might have been done differently to manage his condition, particularly in view of the fact that he was hospitalized two to three weeks before his death and was thought to have a primary psychological illness.

Medical and Psychiatric History. Probably around 1922, while working on the rehearsals of his first opera, *Blue Monday*, George Gershwin began to develop gastrointestinal symptoms, including constipation and indigestion (4). After several medical investigations, it was felt that these symptoms were functional and related to the stressful life Gershwin was leading. The symptoms, which Gershwin referred to as a "composer's stomach," continued despite dietary and other restrictions, and eventually led the composer to undergo psychoanalysis.

Although most writers do not relate those early GI symptoms to Gershwin's fatal brain tumor, Ljunggren (3) did suggest that there was a causal relationship—and that the tumor was probably present for some time before becoming malignant. This relationship does not seem very likely, in my opinion. These symptoms occurred at least fifteen years before the neoplasm manifested itself, and symptoms such as constipation are rarely caused by a cerebral problem. Although Ljunggren (3) emphasized nausea as a prominent GI symptom of Gershwin, Jablonski, who wrote two biographies of Gershwin (5, 6) told me that nausea was not a symptom at all (personal communication from E. Jablonski). Lastly, the brilliance of Gershwin's piano playing was partially due to the deftness, agility, and smooth, rapid motion of his left hand—something which would not be very likely to continue for so long with a right cerebral tumor.

As best as I can determine, Gershwin's fatal tumor first manifested itself on February 11, 1937. He had undergone some personality changes for a few months before, but this may well have been a reactive depression to events in his personal life, and to the fact that he was now working in Hollywood and not New York City. On February 11, Gershwin was playing an all-Gershwin concert with the Los Angeles Symphony Orchestra. While performing his *Concerto in F*, he had a brief lapse and missed a few bars of his music. This lapse was apparently covered over by Alexander Smallens, the conductor, so that most people in the audience did not recognize there was anything wrong. Gershwin was well after a few seconds and was able to continue playing (7). He later told how this episode was accompanied by an unpleasant smell of "burning rubber."

At a rehearsal of the music of *Porgy and Bess* held earlier that day, he was conducting when he was noted to sway and nearly fall from the podium, but there was no alteration in conscious-

From the Department of Neurology, Mount Sinai School of Medicine, New York, NY 10029. Address reprint requests to the author at 127 Union St., Ridgewood, NJ 07450.

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ness and no olfactory hallucinations (8). Gershwin did have a medical checkup after these events and was found to be intact.

He did have a more severe olfactory hallucination with more prolonged behavioral changes while sitting in a barber shop in April 1937. However, he was still writing music well and playing adequately, and still living his stressful but glamorous life.

By June, however, the symptoms had progressed markedly. He became listless, was confused each morning, and was restless and irritable. He developed dizziness and severe headaches and was unable to complete the score for the movie *The Goldwyn Follies*. On two occasions, he was found sitting in a dark room with the shades drawn and could not tell how long he had been there. At times he complained of his environment moving up and down. His symptoms did fluctuate and were somewhat better during a short vacation in Colorado.

Most of his acquaintances and physicians felt that these symptoms were functional, related to the unhappiness in Hollywood, his recent failure in a love affair, and so on. He was also trying to treat his baldness with a mechanical suctioning device which he applied to his head several times a day, and this was thought by some to be causing the headaches as well.

The headaches became more severe, particularly following a dinner party at Irving Berlin's. He became more withdrawn; he had more olfactory hallucinations, and his coordination was impaired. He was first hospitalized on June 23, 1937.

First Hospitalization. It is doubtful that George Gershwin's first hospitalization (June 23 through June 26, 1937) would have been approved by today's utilization review committees. He had been seen by an internist and neurologist before being admitted; the only abnormality they identified was impaired sense of smell in the right nasal passage. An electrocardiogram, skull roentgenograms, visual field examinations, and various blood tests were unremarkable. A lumbar puncture was suggested but declined by Gershwin. He was discharged on June 26, 1937 with this final note on the hospital chart: "Most likely hysteria." Walter Winchell announced on his radio show the next day that Gershwin was "seriously ill."

Gershwin tried working after his discharge but was only partially successful, despite the fact that he was seeing his psychoanalyst daily and had a male nurse in constant attendance. His coordination became more impaired and he found

himself dropping things, spilling foods and liquids, and stumbling, particularly when climbing stairs. His piano playing was particularly affected. The headaches increased, as did the dizzy spells, and the olfactory hallucinations became almost continuous. Returning from a party at Samuel Goldwyn's house one night, he was so ill that he had to sit down on the sidewalk curb for some time (9).

In an attempt to improve symptoms by changing his environment, Gershwin moved into Yip Harburg's vacated cottage on July 4, 1937. Symptoms progressed and there were two episodes of automatisms. In the first, while being driven to an appointment with his psychoanalyst, Gershwin suddenly opened the car door and tried to push the driver out. In the other, Gershwin took a box of chocolates sent to him, crushed the chocolates into a mess, and proceeded to use this mess as a body ointment. He could not say why he performed either of these strange actions and was amnesic for them. It is probable that these episodes were indeed complex partial seizures.

On the afternoon of July 9th, he became drowsy and fell into a semicoma. This led to his final hospital admission.

Second Hospitalization. On his admission on July 9, Gershwin was "comatose," although he did respond to pinprick on the face. There were bilateral papilledema with fresh hemorrhages. He was initially thought to have some facial weakness on the right side and to move the right-sided extremities less than the left (1, 2). Subsequently, bilateral Babinski responses were noted. He underwent a lumbar puncture the day after admission; his spinal fluid pressure was 400 mm with normal protein and cellular contents. The available records do not indicate that his condition was made worse by this diagnostic study.

His family and friends sought neurosurgical consultation elsewhere. Dr. Harvey Cushing, who was first contacted by phone, indicated that he had retired from operative surgery and recommended Dr. Walter Dandy. Dr. Dandy was vacationing on a yacht in the Chesapeake Bay off the coast of Baltimore. Through the influence of the Office of the President of the United States, a Coast Guard cutter brought Dr. Dandy to shore; a privately arranged airplane flew him to Newark Airport, where he awaited air travel to Los Angeles.

Meanwhile, another senior neurosurgeon, Dr. Howard C. Naffziger, was located on vacation in Nevada and was flown to Gershwin's hospital. He felt that Gershwin's condition required immediate, energetic surgical intervention, and after

consultation by phone with Dr. Dandy in Newark Airport, supervised a ventriculogram which showed a right temporal lobe tumor. In an attempt to evacuate this tumor, craniotomy was performed. A cyst was found at surgery with a mural nodule on the medial side. Both operative procedures took about five hours. George Gershwin never regained consciousness. His temperature rose to 106.5°F and he was pronounced dead on July 11, 1937 at 10:35 AM, several hours after the completion of surgery. The report on pathological study was typical for what would be called glioblastoma today.

What Could Have Been Done Differently? It is now over 56 years since the untimely death of George Gershwin and the loss of his great musical creativity and genius, which brought so much pleasure to so many people. Could anything have been done differently to allow perhaps some more creativity to be shared with the world? Probably not in 1937—or even today. Certainly the second admission, which was related to increased intracranial pressure and probable brain herniation, would be difficult to manage even applying today's steroid, hyperosmolar, and other therapies. The survival might have been longer with the deployment of current neurosurgical techniques and postoperative radiation and chemical therapies—but what quality of life would he have enjoyed? Would his creative skills still be present with a damaged right temporal lobe?

On his first admission the diagnosis might have been established. Certainly the irritative nature of the uncinat fits were not well recognized by his physicians so that complete studies were not performed. What further diagnostic tests could have been performed in this first admission in 1937, long before the advent of CT and MRI scans?

Arteriography had been introduced in Portugal in 1926 by Moniz (10). Use of the procedure did not grow by leaps and bounds and it was probably not being performed often in the United States in 1937, although percutaneous carotid angiography was introduced in Boston by Loman and Myerson in 1936 (11). The first published reports of the diagnostic effectiveness of angiography did not appear until after World War II.

Pneumoencephalography with the installation of air from below was first introduced in 1919 by Walter Dandy, the doctor who landed in Newark Airport and consulted on Gershwin's treatment in 1937 (12). However, since Gershwin refused even diagnostic lumbar puncture, it is unlikely that he would have consented to this

much more stressful procedure; the possibility of early increased intracranial pressure might have also contraindicated this procedure.

There was, however, one diagnostic test which might have shed much light on George Gershwin's condition, and this diagnostic test would have been particularly pertinent for demonstrating the seizure activity he was undoubtedly experiencing. Electroencephalography was first introduced in a series of papers by Hans Berger starting in 1929 (13) and became generally accepted after the report by Adrian and Matthews in 1934 (14). A series of articles published in Boston by Gibbs, Lennox, and Davis in 1933–1937 indicated the value of this diagnostic test (15–19). Had this new diagnostic test spread to California in 1937? Apparently not, for things moved much more slowly in the 1930s than in the era of rapid development of new diagnostic tests in the 1970s and 1980s. As an example: I first read of CT scans in 1972; they were commercially available in the New York area in 1974. I did try to determine when electroencephalography became available in the New York area and found that The Mount Sinai Hospital performed its first EEG in March 1939 (personal communication from S. P. Diamond); this test was first utilized at the Neurologic Institute in New York on January 15, 1940 (20).

It is therefore quite unlikely that electroencephalography had spread to California in 1937 or that an EEG facility was available anywhere in that state at that time. This would have been the one diagnostic test, not only to indicate the nature of much of Gershwin's difficulties as a seizure, but also to localize the seizure to the right temporal region, which was otherwise clinically silent. Perhaps early diagnosis would have led to a different kind of therapy earlier, perhaps with more prolonged functional survival. Who knows how many musical masterpieces Gershwin would have turned out after June 1937?

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Case Reports In Dermatology

Case 2-1995

From the Weekly Grand Rounds of the Department of Dermatology at The Mount Sinai Hospital

CYNTHIA M. GERARDI, M.D., AND HIRSHEL KAHN, M.D., PRESENTERS; MARK LEBWOHL, M.D., EDITOR

Case Presentation

Cynthia M. Gerardi and Hirshel Kahn

THE CASE of a 65-year-old woman who had a five-year history of primary biliary cirrhosis was presented at The Mount Sinai Hospital Dermatology Grand Rounds on March 2, 1995. The patient had an extremely pruritic generalized skin eruption and had had it for four years, beginning after the onset of the primary biliary cirrhosis.

A multitude of therapeutic modalities have been employed over the past four years to treat the severe pruritus, all to no avail. Treatment agents have included high-potency topical steroids, sarna lotion, oral atarax, and cholestyramine. Ultraviolet A and B phototherapy (1) three times per week over the past year afforded the patient only slight relief.

On physical examination the patient had diffuse hyperpigmented and depigmented lichenified patches over the face, anterior and posterior trunk, and upper and lower extremities. Superimposed on these lichenified papules were myriad hyperkeratotic papules, most prominently on the trunk and extremities (Figs. 1, 2). Cutaneous examination revealed no other remarkable findings. Biopsy of skin from the upper extremity revealed irregular acanthosis and abundant hyperkeratosis.

Diagnosis: Prurigo nodularis

This reaction pattern occurs in response to repeated scratching and can be seen in patients with chronic itching of any cause.

Discussion

Mark Lebwohl: Would anyone like to comment about the pruritus? That is her main problem, and what are we going to do about it?

Jacob Baral: First of all, the pruritus associated with primary biliary cirrhosis is a well-known entity. It is thought that the increased bile salts in the skin are responsible for the itching. Patients treated with phototherapy have been shown to have had reduction in the serum bile salts. Phototherapy is beneficial in some patients, but not in all of them.

One might also consider using cholestyramine to conjugate with the bile salts.

Irwin Kantor: Ultraviolet therapy is beneficial in patients who are itching from other causes, so the effect that phototherapy has in the pruritus of primary biliary cirrhosis must be nonspecific as well as specific. In addition, the elevated bile salts are thought to have an effect on endorphins rather than a primary effect on the skin.

Mark Lebwohl: Are there any other suggestions for treatment?

Donald Rudikoff: I would try Rifampin in this patient. One study published in *Gastroenterology* (2) reported that 80% of the patients in the series were free of pruritus after three months of treatment. Another option here is Naloxone (3), or the oral form Naltrexate.

James Baral: I suggest a trial of Zostrix,

Adapted from the authors' Grand Rounds presentation at The Mount Sinai Medical Center on March 2, 1995. From the Department of Dermatology, Mount Sinai School of Medicine, New York, NY. Address reprint requests to Mark Lebwohl, M.D., Box 1049, Department of Dermatology, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029.

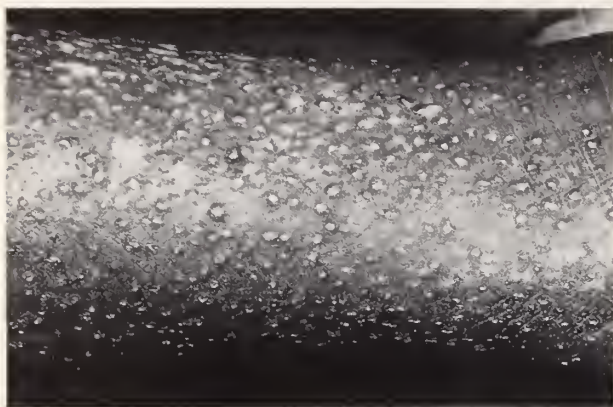


Fig. 1. Patient under discussion: hyperpigmented and depigmented patches, with prominent lichenification and overlying hyperkeratotic papules, on arm.

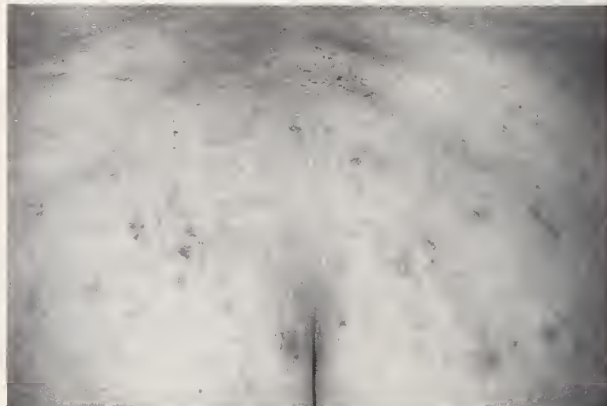
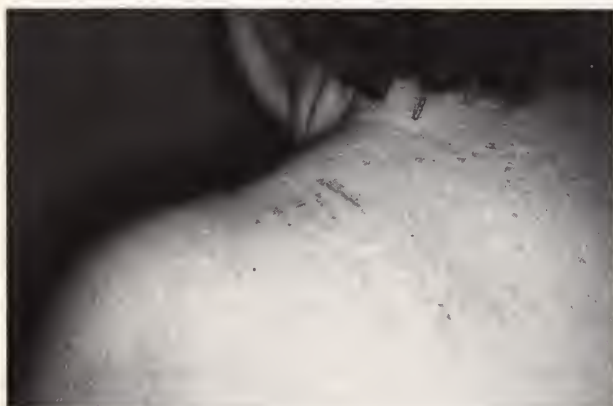


Fig. 2. Another patient with primary biliary cirrhosis. Left Prominent excoriation due to intractable pruritus on upper back. Right Excoriated papules and pigmentary changes on lower back and gluteal area.

which has been shown to be effective in uremic pruritus.

Douglas Altchek: I do not know if Zonalon has been tried in this patient, but it has been effective where other treatments fail.

Treatment Plans

In view of the nature of the patient's underlying liver disease, which is irreversible except by liver transplantation, and the fact that the itching it produces severely restricts the patient's daily activities, her skin condition presents a problem of long-term management.

Rifampicin seems to offer the best prospect for improvement. After two weeks of treatment

with that agent at a dose of 150 mg two times a day, the patient's itching did not abate. The dose was then increased to 300 mg two times a day, but no improvement in the patient's condition has ensued to date.

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Book Reviews

Death and Dignity: Making Choices and Taking Charge

Timothy E. Quill. New York and London: W. W. Norton, 1994. 255 pp. \$21.95. ISBN 0-393-31140-6.

TIMOTHY E. QUILL'S BOOK *Death and Dignity: Making Choices and Taking Charge* forces the reader to confront some very difficult issues. Dr. Quill challenges the reader to question the way we currently deal with decisions affecting the end of life and the kind of death that will result from these decisions. He presents the reader with actual cases illustrating the continuum from an easy death to a hard death. I suspect most of us are uncomfortable thinking about or discussing death, especially our own. The author emphasizes that we need to face the fact that many deaths are not easy. They may be attended by too much pain, even when measures of comfort are actively and creatively employed—a practice Dr. Quill avidly promotes, emphasizing the importance of training physicians to find and use such measures. The price of controlling pain is often lack of consciousness or an impaired ability to think and act, leaving the dying completely dependent on those around them for their every need.

Since this sort of existence is something that most of us would not want, we need to think about and discuss possible changes in the current management of such cases, and more importantly, to think carefully and document how we ourselves would like to be treated should such a fate befall us. In an effort to help us achieve this goal, the author outlines some possible changes that we should consider and perhaps implement, including physician-assisted suicide. Toward furthering such a discussion he, in collaboration with Christine Cassel and Diane Meier, offers rigorous clinical criteria on which to base such a decision. These criteria address many of the concerns often raised when assisted suicide is discussed.

Dr. Quill argues that in the end, what is most important is that each individual deserves the ability to control their own situation. It is they and no one else who must endure any hardships that arise. For some, merely knowing that they have a safe and reliable way to end their suffering, should they so decide, gives them peace of mind, freeing them to enjoy their remaining time to the fullest.

Dr. Quill was launched into the public eye when his article "A Case of Individualized Decision Making" was published in the *New England Journal of Medicine* in 1991. In that article he discussed his decision to write a prescription for barbiturates for a patient diagnosed with acute myelomonocytic leukemia, knowing

she would ultimately use the drugs to end her life. The ramifications of publishing the article, both for Dr. Quill and his patient's family, led him to write this book in an effort to continue and forward the discussion on death and dying.

Death and Dignity reads very well and will resonate for those who believe change is necessary. For those who are as yet unsure, the book offers much to think about.

Allyson L. Robichaud
Bioethics Education
Mount Sinai School of Medicine

Death Notification

R. Moroni Leash. Hinesburg: Upper Access, 1994. (Book orders: 1-800-356-9315.) 278 pp, index. Paper. \$19.95. ISBN 0-942679-08-3.

THIS BOOK is easy to read. More important, it contains extremely useful information in the form of case reports followed by well-thought-out comments. I assume that most of the case reports derive from the author's direct personal experiences while serving as a clinical social worker at the University of California, Davis, Medical Center, said to be the busiest trauma center in the United States. Leash is currently employed by the Kaiser Foundation Hospitals in Sacramento, where he provides grief and crisis counseling.

The book is divided into three parts, each of which contains several chapters. The book is well referenced and indexed. I was intrigued by the detail provided by the author with respect to the extent of the data obtained from the survey instruments which were used. While the author notes the weaknesses in his method of data collection, his variety of anecdotal details and obvious extensive experience provide sufficient information regarding the need to be attentive to the sensitivities of the moment and pitfalls to be avoided.

The first part deals with the process of notification of the next of kin. While I have no quarrel with designating the physician as the primary contact for a detailed medical explanation, in actual practice this is not realistic with respect to the initial news, and perhaps even some of the substantive aspects. This is particularly so if the individual was not treated in the hospital, or if the next of kin are not relatively close. The complexities are well addressed. A sensible section deals with the process of debriefing family and family contacts, and the need to provide for preparing the body for viewing by the family. In this time of severe organ shortages, the question of when and how to discuss organ and tissue donation is dealt with quite appropri-

ately, as I would expect from an individual with a great deal of experience with trauma victims. However, the section dealing with consent for autopsy is too simplistic to be of much value or effect.

Several separate sections are devoted to the death of an infant or a child, and especially how to talk to young children regarding the death of a parent. Finally, a most important and revealing section deals with the physician's responsibility on delivering a terminal diagnosis, not only to a family member, but to the patient. How this is done is the ultimate mark of a compassionate and caring physician. The author stresses the importance of establishing what the patient and the family already know, even to the extent of summarizing information that may have been given to them previously. The need for truth, "without brutalizing someone with it," and for trust, is paramount, and the difference between the right to know and the duty to know is highlighted. "With proper management of the process, no persons need remain in the traumatic situation of either being denied the information they desire, or having it thrust upon them in spite of their contrary wishes." The practical application of this principle is well elucidated.

All of us need guidance in approaching the turmoil associated with the death of someone close. I recommend this book for those who want such help and guidance to maintain sensible and realistic sensitivity.

Sherman Kupfer, M.D.
Department of Medicine
Mount Sinai School of Medicine

You Don't Have to Suffer: A Complete Guide to Relieving Cancer Pain for Patients and Their Families

Susan S. Lang and Richard B. Patt, M.D. New York and Oxford: Oxford University Press, 1994. 366 pp. \$25.00. ISBN 0-19-508418-7.

PAIN is one of the most common and most distressing symptoms of cancer. In a recent survey of over 1,300 cancer patients published in the *New England Journal of Medicine* (March 3, 1994), about two-thirds of the patients reported experiencing pain, and in one-third pain was severe enough to impair function. More importantly, it was estimated that 42% of these patients were not receiving adequate analgesia. This book is therefore a welcome and useful guide, providing a wealth of information and advice for cancer patients and their families.

Susan S. Lang is a senior science writer at Cornell University, and co-author Dr. Richard B. Patt is deputy chief of the Pain Service at the M. D. Anderson Cancer Center in Houston. The book is subdivided into three parts. Part I ("Cancer and Its Pain") is a review of the different mechanisms of pain and includes assessment and evaluation of pain. The authors quite appropriately succeed in demystifying pain and the use of an-

algesics, explaining why fear of addiction to painkillers is inappropriate. One of the crucial messages of this book is the importance of communication in the doctor-patient relationship, wisely described in the two paragraphs entitled "Complying with the doctor's recommendations" and "On being an active health-care consumer." The clear message is: do not underestimate pain, and do not undertreat.

Part II ("The Painkillers") is a detailed yet clear and concise description of the different classes of pain medications, based on the World Health Organization's "analgesic ladder." It is a mini-PDR with a complete and thorough list of drugs, their doses, onset and length of action, and equivalent doses.

Part III ("Other Approaches and Concerns") addresses side effects and how to deal with them. It includes also special sections on "mind-body" approaches, such as relaxation and imaginary techniques, which are increasingly popular. The extraordinary difficulties of the terminal period, as well as the recently publicized issues of euthanasia, are also discussed.

This book should be read by cancer patients (or their relatives) experiencing unrelieved pain, as well as by health care professionals dealing with cancer patients.

A. Philippe Chahinian, M.D.
Division of Neoplastic Diseases
Department of Medicine
Mount Sinai School of Medicine

When the Body Speaks Its Mind

Berney Goodman. New York: J. P. Tarcher/Putnam, 1994. 226 pp. \$23.95. ISBN 0-087477-758-5.

I MUST CONFESS to the reader that I have known Dr. Goodman for many years. Perhaps that has influenced me in accepting the task to review his book. It is not a medical text so it is easy to carry around. Happily, the book is easy to read and is as entertaining as it is informative. It is divided into several sections, including a preamble which serves as an introduction and a concluding section which provides the reader with some of the author's personal thoughts. More about that later.

Part one deals with a discussion of the psychiatrist's role as a detective in ferreting out the significance of the patient's descriptions of thoughts and moods. I suspect that the author did not intend to describe the detective's role as unique to psychiatry, since understanding the significance of whatever the patient tells a physician is the kernel of the interaction between the patient and the physician. Yes, the physical examination and the laboratory can document pathophysiology, which may or may not help in ascertaining clinical relevance. In some instances, unfortunately, these "objective" results may be misleading. But the author does a superb job in telling us how important it is to listen to the patient. He defines the language of

somatization succinctly and provides wonderful examples from his broad clinical experience. This takes us through the first two parts, and leads directly to his elucidation of the serious and extreme nature of the Munchausen syndrome in its several varieties. These cases, too, are described with clarity. I think that I would want to be a little more optimistic about the possibility of truly helping these unfortunate people rather than categorizing them as incurable. It was not so long ago that some diseases were considered incurable, and in those which might still be, we have seen some progress in arresting progression and relieving pain. Clearly, what is needed is research, but Dr. Goodman does not provide the reader with any insight into why or how this might be impossible in this serious disease.

The final and brief chapter is devoted to Dr. Goodman's afterthoughts and feelings, and is labeled as such. He comments on the societal impact of the increased attention to and care of the body and mind. I enjoyed that section as well, particularly his confession, amongst several, of his fallibility and the need to say "I don't know." This, too, must be appreciated by all physicians. I recall the story about a surgeon who, after an operation, met the parents in the visitor's lounge and triumphantly reported that their son would play the violin again. "But doctor," they said, "he never played the violin."

I have not checked out all of the referenced sources, but the paucity of recent material reinforces the notion that not much in the way of research of any sort is being done on Munchausen syndrome and factitious disorders. Factitious disorders are described ever so briefly in the 1994 DSM IV. Thus, Dr. Goodman's experiences are well worth the reader's efforts and do serve as a good place from which to start to gain some insight into this problem.

In summary, I can recommend this book to my colleagues and to trainees and students. The experiences and thoughts of a sensitive, warmly human master clinician always are timely and timeless.

Sherman Kupfer, M.D.
Department of Medicine
Mount Sinai School of Medicine

Girl, Interrupted

Susanna Kaysen. New York: Vantage Books, 1994. 168 pp. Paper. \$10. ISBN 0-679-74604-8.

A VAST AUTOBIOGRAPHICAL LITERATURE has been written about authors' experiences in asylums and psychiatric wards. The reader may begin each work in this genre with hope, anticipating the literary tension between confusion and clarity, normalcy and artistic imagination. Susanna Kaysen's *Girl, Interrupted* is the latest addition to this body of literature, one which has already achieved some level of popularity and acclaim.

Susanna Kaysen was admitted to McLean Hospi-

tal, one of the best psychiatric facilities in America, in the late 1960s when she was 18 years old. An admission referral note points to profound depression, suicidality, and a troubling ambivalence suggested by her statement that she would either kill herself or get pregnant. She was given a diagnosis of borderline personality and remained hospitalized for the next two years. *Girl, Interrupted* is a collection of anecdotes and sketches that cover the two-year admission. As these vignettes unfold, one senses two stories, what Freud might call the manifest and the latent.

The tone and the content of the manifest material are highly reminiscent of many such works that have appeared over the years. There is an assumption that most of the staff are self-serving and that the patients suffer as a consequence. The patients are presented as relatively sane in an insane world; they may possess deeper insight and understanding than the staff. This is best exemplified by a story in which the young women patients had some foreknowledge of Nixon's "plumbers," the former CIA agents who performed covert actions for the President, including the Watergate breakin. The nurses, we are told, dismissed the concerns about these dangerous operatives as delusional material. We are also treated to the author's version of a visit by Nobel Laureate James Watson, who sounds emotionally and intellectually adrift compared to the solid common sense of the patient. When another patient wraps an entire room in yards and yards of toilet paper, the author describes the scene as "magnificent." It is clearly viewed as an act of liberation.

The actions of the hospital staff, particularly the psychiatrists, on the other hand, demonstrate great insensitivity. The author does not go beyond brief, clipped portrayals of staff indifference or cruelty. The following dialogue is purportedly a "representative conversation":

"The head nurse said you were acting out after lunch yesterday."

"She's making that up."

"Hmmm . . . Hostility." He scribbles in a notebook.

"Can I have orders for Tylenol instead of aspirin?"

"There's no difference."

"Aspirin gives me a stomach ache."

"Are you having headaches?"

"This is in case I do."

"Hmmm . . . Hypochondria." He scribbles again.

This is the only interaction between the patient and a resident psychiatrist reported by the author for the entire admission.

So here is the author 25 years later depicting a system which seems based on an unfair and irrational "interruption" of people's lives. Psychiatrists and nurses are jailers, patients are the victims. But the latent story here is both more complex and more hopeful. There is a transition from a highly disturbed adolescent without direction or drive to a highly accomplished writer, a truly functional human being. It is unfortunate that the ingredients of this change can

only be guessed at because *Girl, Interrupted* lingers on the recalcitrant attitude of the author as a disturbed adolescent. It may require more reflection before the author can present the fuller story, one which portrays her two-year hospitalization and her emotional struggles in their real complexity.

Michael J. Serby, M.D.
Department of Psychiatry
Mount Sinai School of Medicine

Health and Numbers: Basic Biostatistical Methods

Chap T. Le and James R. Boen. New York: Wiley-Liss, 1995. 247 pp, ill. Paper. \$34.95. ISBN 0-471-01248-3.

THIS REVIEW is a joint effort by a first-year medical student taking a course in epidemiology and biostatistics and a faculty member who teaches the course.

The word "statistics" chills the hearts of a statistically significant number of medical students. Whether this chill is based on a barefaced fear of numbers, or on a certainty that the subject will pale in comparison with the immediate charms of gross anatomy, many medical students approach the required introductory course in biostatistics with little enthusiasm. Le and Boen's *Health and Numbers: Basic Statistical Methods* seems to have been written with these students, particularly the more phobic ones, in mind.

The text begins with a soothing introduction designed to reassure frightened beginners that the mathematics required for statistics will not kill them. The authors admit that while statistics is a scary subject, the fear can be overcome. Le and Boen assert that the problems the subject poses for many are all reducible to navigating "the distribution of numbers one cannot see" and translating formulas that are really just recipes for cooking up numbers—recipes that are written in a foreign language. The text proposes to ease the way past these difficulties and does much to accomplish just that.

Health and Numbers logically and clearly tackles the basic concepts and tools of statistics, including probability, confidence estimation, and basic hypothesis testing. These concepts are introduced with little fanfare and as simply as possible. Probability is described as a way "science and scientists cope with uncertainty." Formulas and calculations are presented early in the discussion of each subject and are immediately put to use in several sample problems. Examples dominate the text and are perhaps its best feature. For

the beginning student of statistics the systematic navigation through problems that the authors offer allows ample opportunity to practice the use of the basic formulas and concepts. It seems likely that any student approaching a problem will find it mapped out in this text in a helpful and clear way. Furthermore, the book lends itself to use as a reference text. A student wondering, "When do I use a one-tailed test and when do I use a two-tailed test?" can find this and other questions answered straightforwardly in the text without wading through too many practical examples and lengthy explanations.

Overall, the text is a well-designed aid to problem set solving, and therein may lie its faults. In an effort to help students over their fears of formulas and statistical principles, the authors have perhaps moved the tools too far away from the trade. Although examples are often used, and phrases such as "prevalence rates of hypertension" and "cholesterol values" abound in the text, the actual usefulness of statistical evaluation and convincing presentation of data are understressed. The authors offer the book as an introduction, and relegate study design and practical application of the nuts and bolts of statistics to a higher level of proficiency than they hope to teach. Even so, without a basis in practice, the text limits itself to being more of an introduction to doing statistics homework than to statistics itself and its usefulness as a discipline.

For this reason the text may be limited in its utility to medical students, who must learn to apply statistical mathematics and concepts to an understanding of the medical literature. The book has only a certain limited usefulness to those struggling with calculations, and would be best used as a supplemental text for those students needing such introductory help.

From the point of view of a faculty member, several concerns arise. Many important epidemiologic concepts are alluded to but are either barely explained or not explained at all. Like many first editions, this book has typographical errors, including references to the wrong tables and incomplete references, that may confuse students.

This book does not really fill a gap. For a briefer and clearer introduction to basic statistics, try *Statistics at Square One* by Swinscow. Several excellent books cover some of the same topics plus epidemiologic concepts, including *Clinical Epidemiology* by D. Sackett et al.

Andrea Gottsegen
Henry S. Sacks, Ph.D., M.D.
Dept. of Community Medicine and
Biomathematical Sciences
Mount Sinai School of Medicine

The Mount Sinai Journal of Medicine Awards 1994

Ralph Colp Prize

The 1994 Ralph Colp Prize for best surgical paper published in *The Mount Sinai Journal* during the calendar year went to Ellen G. Polokoff, M.D., Richard J. Knight, M.D., Harry Schanzer, M.D., and Lewis Burrows, M.D., for their article "En Bloc Transplantation of Infant and Child Cadaver Kidneys to Adult Recipients" (vol. 61, no. 1). The award was established by colleagues and friends of Ralph Colp, distinguished surgeon and for many years chief of surgery at The Mount Sinai Hospital. All *Journal* awards are juried by a committee of five members of the publication's Editorial Board and are presented at the annual Prize Ceremony at the Mount Sinai School of Medicine. The ceremony for the 1994 awards was held on May 19, 1995.

Globus Prize

The 1994 Globus Prize for the best paper with a clinical orientation published in this journal during the calendar year went to Michael J. Paidas, M.D., Michael J. Haut, M.D., and Charles J. Lockwood, M.D., for their article "Platelet Disorders in Pregnancy: Implications for Mother and Fetus" (vol. 61, no. 5). This award honors Joseph H. Globus, founder and first editor-in-chief (1934–1952) of *The Mount Sinai Journal*.

Student Prize

No award was made for the 1994 Student Prize for the best student paper published in this journal during the calendar year.

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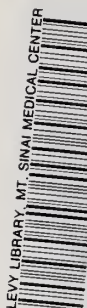
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Introduction

PAUL L. GILBERT, M.D.
Associate Professor
Department of Medicine
Mount Sinai School of Medicine

Screening in the New Environment of Medicine: Colon and Prostate Cancer

AS A PRACTITIONER, I must constantly deal with people who want to be screened for cancer. Two of the cancers they are most concerned about are cancer of the colon and cancer of the prostate. There are as many opinions on what kind of screening should be done for each of these carcinomas as there are physicians practicing, and the current literature on both colonoscopy and prostate-specific antigen testing is wide.

Both diseases are easily diagnosed, and both are potentially curable. If untreated, both can kill. However, managed health care companies are now preaching cost-effective medicine. We must be able to separate the idea of cost-effectiveness from the idea of cheapness—the two are not always the same. Interestingly, the various Canadian medical societies do not recommend either colonoscopy or prostate-specific antigen testing.

About 160,000 new cases of colon cancer occur each year, and 60,000 people with colon cancer are going to die because of it. People over age 50 have a 5% chance of developing this cancer, and once having developed it, a 25% chance of dying from it. Steven Itzkowitz, of the Division of Gastroenterology, Mount Sinai School of Medicine, discusses screening for carcinoma of the colon.

About a quarter of a million men develop prostate cancer each year, but the death rate is not increasing anywhere near what the discovery rate is. Alexander Kirschenbaum of the Department of Urology at Mount Sinai School of Medicine discusses how internists should be screening for prostate cancer, rather than setting up booths at fairs and doing free prostate-specific antigen tests and referring patients back to the hospital, as is occurring in New Jersey.

Adapted from the Grand Rounds presentation "Screening for Cancer in the New Environment of Medicine" at the Mount Sinai School of Medicine on November 1, 1994.

Screening in the New Environment of Medicine:

Colon Cancer

STEVEN H. ITZKOWITZ, M.D.

COLORECTAL CANCER is a major cause of morbidity and mortality in the United States. Fortunately, this disease has a well-defined premalignant phase, and even early-stage cancers that are detected have a favorable prognosis. Screening for colorectal cancer would therefore seem reasonable. An effective screening program should reduce mortality from colorectal cancer, and recent data do in fact attest to the effectiveness of colon cancer screening in reducing mortality.

Screening Average-Risk Individuals

The concept of screening for colorectal cancer is usually considered in the context of the general population. For screening such average-risk individuals, the National Cancer Institute (NCI), the American Cancer Society (ACS), and the American College of Physicians (ACP) have all endorsed a colon cancer screening program that begins at age 50 with annual fecal occult blood testing (FOBT) and includes sigmoidoscopy every 3–5 years (1). Age 50 has been chosen as the starting point of screening because the incidence of colon cancer begins to increase at approximately that age.

Fecal Occult Blood Testing. Historically, the most commonly used test for occult fecal blood has been the guaiac-based Hemoccult test (reviewed

in 2). The biochemical principle behind this test is that peroxidase activity in the stool oxidizes the guaiac reagent to a blue color when hydrogen peroxide in the developing solution is added. Hemoglobin has pseudoperoxidase activity, which accounts for its ability to produce a positive result on Hemoccult testing. If hemoglobin becomes degraded or denatured, it loses its pseudoperoxidase activity, so bleeding from the upper gastrointestinal tract, or even colonic bleeding with prolonged transit time, can result in a false-negative Hemoccult test. For the same reason, once stool smears are prepared on Hemoccult cards, storage for a prolonged period (more than a few days) can result in false-negative results. Other causes of a false-negative Hemoccult test are ingestion of vitamin C (which has antioxidant activity), intermittently bleeding or nonulcerated colonic neoplasms, improper sampling by the patient.

False-positive Hemoccults can be due to ingestion of exogenous peroxidases (such as red meat or certain fruits and vegetables rich in vegetable peroxidase), ingestion of aspirin and nonsteroidal antiinflammatory drugs (which can nonspecifically produce low-grade blood loss), use of topical iodine solutions, and rehydration of Hemoccult cards (placing a drop of water on the card just prior to adding the developing solution).

In individuals with known colorectal cancer, Hemoccult sensitivity is 50%–70%, which can be increased to 90% if slides are rehydrated (2). Since significant blood loss from an adenomatous polyp is rare unless it is large, most adenomas are found serendipitously in the course of evaluating a Hemoccult-positive stool. Specificity of Hemoccult is 99% (3).

Five controlled trials of FOBT in colorectal cancer have been conducted; three are still in

Adapted from the author's Grand Rounds presentation at The Mount Sinai School of Medicine on November 1, 1994. From the Division of Gastroenterology, Mount Sinai School of Medicine, New York, NY. Address reprint requests to Steven H. Itzkowitz, M.D., Associate Professor of Medicine, Division of Gastroenterology, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1069, New York, NY 10029.

progress (4). These studies are remarkably similar in several respects (Table 1). First, the frequency of FOBT positivity in asymptomatic individuals is approximately 1%–2%. Second, the positive predictive value for finding a colorectal neoplasm (adenoma or cancer) based on a positive FOBT is 22%–58%. Third, all studies have found cancers in the screened group that are at earlier stages than those found in the nonscreened controls. Whether the detection of earlier stages of colon cancers by screening will translate into improved mortality is not yet known for all studies.

To date, only the two studies from the United States have come to completion, and both suggest an improved survival rate in individuals screened by FOBT. The trial from the Memorial Sloan-Kettering Cancer Center/Strang Clinic in New York involved two groups of patients; both groups received rigid sigmoidoscopy, but the study group also underwent FOBT (4). Over a 10-year follow-up period, a 43% reduction in mortality was observed in the study group. The study from the University of Minnesota enrolled 46,551 participants aged 50–80 years who were randomly assigned to one of three groups: yearly FOBT (using Hemoccult cards), biennial FOBT, or a control group that did not receive Hemoccult cards (5). After a follow-up period of 13 years, the cumulative mortality from colorectal cancer was reduced by 33% in the annual FOBT group compared to the control group, whereas no survival advantage was observed in the biennially screened group. A limitation of this study is that 83% of Hemoccult cards were rehydrated, a process known to increase both the total positivity rate of the test and the false-positive rate. Thus, although rehydration improved the sensitivity rate from 81% to 92%, this improvement came at the expense of a decrease in specificity from 98% to 90%, and a consequent decrease in the positive predictive value from 5.6% to 2.2%. The higher sensitivity

generated a 38% rate of colonoscopy, which, some have argued, contributed more to the beneficial outcome than did FOBT. Confirmation of the impact of FOBT screening on colorectal cancer mortality must await the maturation of the three European controlled trials still in progress.

Newer FOBTs have been developed based on an immunoassay which uses an antibody to detect human-derived hemoglobin. Conceptually, the advantage of these tests is the lack of interference by exogenous peroxidases or agents such as vitamin C and iodine that affect the biochemical guaiac reaction. Preliminary studies indicate that immunoassays for occult blood are more sensitive than guaiac-based tests (6), but data are not yet available on efficacy for screening large, asymptomatic populations.

To perform the Hemoccult test, the subject should be instructed to place a thin stool smear on both windows of a card, and do this for three consecutive bowel movements (total three cards, six windows). It is fair to sample an area of the stool that contains blood. As soon as possible after the last card is prepared, they should be submitted for developing; delays created by returning cards in the mail should be avoided. For two days prior, and during the course of preparing the cards, individuals should avoid ingesting red meat, peroxidase-rich fruits and vegetables, vitamin C, aspirin, and nonsteroidal anti-inflammatory drugs. A positive Hemoccult test is one in which even one window out of six is positive.

Evaluative studies of patients whose Hemoccult test is positive depend on whether the individual is truly asymptomatic. In symptomatic patients, the studies are appropriately directed by the clinical suspicion. If the individual is indeed asymptomatic, the initial evaluation should begin with colonoscopy, since this is both diagnostic and potentially therapeutic. Upper gastrointestinal tract abnormalities account for only 10% of positive Hemoccult tests.

TABLE 1
Controlled Trials of Colorectal Cancer Screening by Fecal Occult Blood Test

Site	Cohort size	Positivity rate (%)	Predictive value (%) (Ade + Ca)	Dukes' A&B Ca (%)	
				Screened	Controls
Goteborg, Sweden	27,000	1.9	22	65	33
Nottingham, UK	150,000	2.1	53	90	40
New York, USA	22,000	1.7	30	65	33
Minnesota, USA	46,551	2.4	31	78	35
Fuhnen, Denmark	62,000	1.0	58	81	55

Ade, adenomas.

Adapted from Winawer et al. *J Natl Cancer Inst* 1991; 83:243–253.

Sigmoidoscopy. To date, there are no prospective, controlled trials of sigmoidoscopy for screening for colorectal cancer. Two case-control studies, however, have suggested a reduction of mortality of 60%–70% for cancers within the reach of the instrument (7, 8). The larger study examined the effects of rigid sigmoidoscopy during the 10-year period before the diagnosis of fatal rectal cancer in 261 cases, compared to 868 matched controls (7). Even after adjusting for confounding factors (such as health consciousness), sigmoidoscopy seemed to reduce mortality by 59%–75%, and this beneficial effect seemed to apply even if sigmoidoscopy was performed only once in 10 years. A similar reduction in rectal cancer mortality was noted in the second case-control study, which analyzed individuals screened by either rigid or flexible sigmoidoscopy (8).

Identifying High-Risk Individuals

The following conditions are associated with high risk for colorectal cancer:

- **Hereditary colon cancer syndromes**
 - Familial adenomatous polyposis (FAP)
 - Attenuated adenomatous polyposis coli (AAPC)
 - Hereditary nonpolyposis colorectal cancer (HNPCC)
- **Family history of colorectal cancer or adenomas**
- **Personal history of colorectal cancer or adenomas**
- **Inflammatory bowel disease**
 - Ulcerative colitis
 - Crohn's colitis

Only the role of heredity is considered here.

Hereditary Colon Cancer Syndromes. The hereditary colon cancer syndromes—two forms of polyposis and one that is not a form of polyposis—are inherited in an autosomal dominant pattern.

Familial Adenomatous Polyposis. Familial adenomatous polyposis (FAP) is characterized by the development of hundreds to thousands of colonic adenomatous polyps, usually appearing in adolescence and almost always present by age 35–40 (9) (Table 2). Colon cancer is inevitable if the colon is not removed: the average age at cancer diagnosis is 39 years. Colon cancers arising in individuals with FAP account for approximately 1% of the total colon cancer burden in the United States.

Patients with FAP are prone to extracolonic neoplasms. Polyps of the upper gastrointestinal tract are common. Duodenal polyps, found in up to 90% of FAP patients, are adenomas and therefore carry malignant potential. The estimated lifetime risk of duodenal adenocarcinoma, which is often periampullary, is 4%–12%, making it a significant cause of death in patients with FAP who have already undergone prophylactic colectomy. Gardner's syndrome, characterized by intestinal adenomas plus other extraintestinal growths, such as mandibular osteomas, skin cysts, dental abnormalities, desmoid tumors, and congenital hypertrophy of retinal pigment epithelium was once assumed to be a distinct syndrome but is now considered part of the FAP syndrome.

The APC (adenomatous polyposis coli) gene has been localized to chromosome 5q21, and numerous mutations have been described. Despite many different gene mutations, the common result is a truncated APC protein. Based on this, genetic testing for APC mutations has become a reality (10, 11).

TABLE 2
Features of Hereditary Colorectal Cancer (CRC) Syndromes

	FAP	AAPC	HNPCC
Age at CRC dx (mean)	39	55	48
Distribution	random	mainly right side	mainly right side
No. of polyps	>100	1–100	<10
Distribution of polyps	left or universal	mainly right side	mainly right side
Other cancers	duodenal; ampullary	periampullary	endometrium; stomach; small intestine; biliary; GU
Gene (chromosome)	APC (5q21)	APC (5q21)	hMSH2 (2p) hMLH1 (3p) hPMS1 (2q) hPMS2 (7p)

FAP, familial adenomatous polyposis; AAPC, attenuated adenomatous polyposis coli; HNPCC, hereditary nonpolyposis colorectal cancer; APC, adenomatous polyposis coli

Attenuated Adenomatous Polyposis Coli.

Another hereditary colon cancer syndrome, termed attenuated adenomatous polyposis coli (AAPC), has recently been described (Table 2). This autosomal dominantly inherited syndrome, originally called hereditary flat adenoma syndrome (12), is characterized by multiple colonic adenomas, usually less than 100 in number, that assume a proximal predominance and have a flat rather than polypoid growth pattern. Colon cancers in this syndrome occur later (mean age 55) than in other hereditary syndromes. The genetic defect in this syndrome is a marked truncation of the APC gene, confirming that the syndrome is a variant of familial polyposis. Recent studies indicate that the spectrum of upper gastrointestinal pathology (gastric fundal gland polyps, duodenal adenomas, periampullary carcinoma) in AAPC is identical to that in APC, suggesting that clinical attention must also be directed to the upper gastrointestinal tract in these patients (13).

Hereditary Nonpolyposis Colorectal Cancer.

HNPCC syndromes are characterized by the development of colorectal cancer without polyposis (12). Previously referred to as Lynch syndromes I (site-specific colorectal cancer) and II (cancer family syndrome), HNPCC syndromes account for approximately 4%–6% of all colorectal cancers in this country.

The International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer has proposed the following criteria (known as the "Amsterdam Criteria") for the definition of HNPCC: (a) three or more relatives with histologically verified colorectal cancer, one of whom is a first-degree relative of the other two; (b) colorectal cancer involving at least two generations; and (c) one or more cases of colorectal cancer developing prior to age 50 (14). The colon cancers that arise in HNPCC individuals are marked by predominance in the proximal colon, a greater than expected incidence of multiple primary colon cancers, and an average age at cancer diagnosis of 48 years (Table 2). Colonic adenomas occur in approximately 20% of individuals with HNPCC, no greater than in the general population. Extracolonic cancers are the hallmark of the Lynch syndrome II variant of HNPCC, carcinoma of the endometrium, stomach, small intestine, biliary tract, kidney, ureter, and ovary being the most common. Thus, when taking a family history of "colon cancer," one should specifically inquire about a family history of other types of cancers as well.

The recent discovery of some of the genes responsible for HNPCC will, it is hoped, permit fu-

ture clarification of the clinical definition of these syndromes. To date, four genes that appear to contribute to HNPCC have been discovered (Table 2). These genes play a role in repairing DNA mismatches, so that mutations or loss of these genes set the stage for many other gene mutations. Although genetic testing for each of these genes should be forthcoming, there are kindreds with HNPCC who do not have abnormalities of these genes, suggesting that other genes may also be responsible for HNPCC.

Familial Colorectal Cancer. "Syndromic" colorectal cancers account for approximately 5% of all colorectal cancers in the United States, and it has been assumed that the other 95% of cases are sporadic cases. However, the assumption is misleading, since inherited factors may play a role in these cases as well. For example, genetic epidemiology studies have consistently shown a two-to-three-fold increased risk for colon cancer among first-degree relatives of patients with either colon cancer or colon adenomas, and a similar increased risk for colon adenomas among first-degree relatives of those with adenomas (9). Studies of large kindreds indicate that indeed there is an inherited susceptibility to colonic neoplasms. Adenomatous polyps were found in 19% of kindred members, compared to 12% of spouse controls. Pedigree analysis indicated an autosomal dominant, partially penetrant pattern of inheritance for colonic neoplasms (9). Thus, it is estimated that perhaps half of all so-called "sporadic" colon cancers may indeed have an underlying genetic susceptibility.

Screening Guidelines for Hereditary and Familial Colorectal Cancer

Suggested guidelines for colorectal cancer screening are based on genetic risk (Table 3).

Flexible sigmoidoscopy should be performed in all first-degree relatives (parent, sibling, child) of individuals with FAP, beginning in adolescence but continuing into adulthood. Genetic testing of peripheral blood lymphocyte DNA is now available and can be used to determine if a family member has inherited the mutant gene. Studies indicate that using appropriate DNA markers yields extremely high accuracy for determining whether an individual is affected with FAP. Individuals who test positive or indefinite should be screened as described. Until longitudinal studies validate the reliability of genetic marker testing, subjects who test negative should still be screened by flexible sigmoidoscopy, perhaps every 3 years.

TABLE 3
Screening Recommendations Based on Genetic Risk*

	Age to begin screening (yrs)	Method	Frequency
FAP syndromes	10–12	Flex sigmoidoscopy	Yearly to age 40, then every 3 yr
HNPCC syndromes	25‡	Colonoscopy FOBT	q 2 yr to age 35, then yearly
First-degree relative† One	35–40	Standard: Flex sigmoidoscopy FOBT	q 3–5 yr yearly
More than one	35–40‡	Colonoscopy FOBT	q 3–5 yr yearly

* Consensus recommendations by the American Gastroenterological Association and the American Society of Gastrointestinal Endoscopy.

† Parent, sibling, or child.

‡ Or 5 years younger than earliest age at diagnosis of colon cancer in family, whichever comes first.

Patients who have AAPC may have only a few adenomas with more proximal locations; for that reason, colonoscopy rather than flexible sigmoidoscopy should be the preferred screening method. Genetic testing for AAPC, while feasible, has not been well studied.

Individuals who belong to an HNPCC kindred should have annual fecal occult blood testing and full colonoscopy every 2 years, beginning either at age 25 or at the age 5 years younger than the earliest colon cancer diagnosis in the family. Although several DNA repair genes have been implicated in HNPCC, DNA genetic testing is not currently available.

For individuals with one first-degree relative (defined as parent, sibling, or child) who has colorectal cancer, standard screening—yearly fecal occult blood testing and flexible sigmoidoscopy every 3–5 years—should be performed, but should be instituted at age 35–40. In those persons who have more than one affected first-degree relative, colonoscopy should replace flexible sigmoidoscopy, beginning either at age 35–40 or when the person is 5 years younger than the earliest age at diagnosis of colon cancer in the relative, whichever comes first.

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Screening in the New Environment of Medicine:

Prostate Cancer

ALEXANDER KIRSCHENBAUM, M.D.

PROSTATE CANCER is the second leading cause of cancer deaths in American men. Both the incidence of prostate cancer and the mortality from this disease are rising. In 1988, there were 90,000 newly diagnosed cases and 26,000 reported deaths from prostate cancer. In 1994, there were over 200,000 newly reported cases and 38,000 deaths attributable to this disease (1). This phenomenon can be explained by an increase in longevity of the population, a decrease in the death rate secondary to concurrent illnesses, and the introduction of new screening modalities.

The screening population is defined as the patient population chosen at random. Patients who come to physicians' offices (for medical or urologic evaluation) are not considered members of a screening population. The detection rate of cancer of the prostate in a screening population was 2.5% (2); the detection rate in a select group of patients who come to a physician's office for urologic evaluation was 15% (3).

The goal of any screening is to reduce mortality from the disease for which the screening is being carried out. Because no curative therapies for advanced prostate cancer are available, screening offers the hope of detecting cancers while they are still organ confined and potentially curable. The survival rates for men with organ-confined prostate cancer treated with radical prostatectomy are equivalent to those of age-matched patients without prostate cancer (4).

However, other data argue against aggressive screening. More men with prostate cancer die from other causes than from the prostate cancer itself. The prevalence of microscopic prostate cancer is 30% in men over 50 years of age (5). Only a small percentage of these patients will develop clinically significant disease. At present, there are no reliable tests that distinguish aggressive prostate cancers from biologically inert disease. Prostate cancers are generally slow-growing tumors. It has been estimated that the doubling time of small, organ-confined prostate cancer is approximately 4 years. Thus, it would take 15 years or more for a 1-cc volume tumor to become life-threatening (6). Therefore, aggressive screening should be reserved for those patients with longer life expectancies.

It is estimated that the ideal screening test should have a sensitivity, specificity, and negative predictive value of over 90%, a false-negative rate under 10%, and a false-positive rate under 20%. More important, such an ideal test should predict the biological behavior of the tumor. Even a combination of all currently available screening tests would not approach this ideal for screening prostate cancer.

Screening Tests for Prostate Cancer

Digital Rectal Examination

Prostate cancer is detectable by digital rectal examination in the screening population in approximately 1.4% of patients (7). Fifty percent of men classed as positive (induration or nodules) by rectal examination were subsequently found to have cancer of the prostate (8). The calculated

Adapted from the author's Grand Rounds presentations at Mount Sinai School of Medicine on November 1, 1994. From the Department of Urology, Mount Sinai School of Medicine, New York, NY. Address reprint requests to Alexander Kirschenbaum, M.D., Associate Professor of Urology, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1272, New York, NY 10029.

sensitivity and specificity of digital rectal exams are 55%–69% and 89%–97%. Based on varying prevalence rates of prostate cancer, positive predictive values range from 11% to 26% and negative predictive values range from 85% to 96% (9). However, it appears that the negative predictive value of digital rectal exam has been overestimated. There is a large population of patients with elevated serum prostate-specific antigen (PSA) values, but negative digital rectal exams, who have biopsy-proven cancer of the prostate.

Digital rectal examination is a subjective test. Variations in skill between individual examiners further reduce both the negative and positive predictive values of this technique. The American Cancer Society recommends annual digital rectal examination in all men over forty years of age. There is an increased rate of detection of cancer of the prostate when digital rectal examination is performed early in patients' lives and in a routine fashion. However, there is no evidence that screening by digital rectal examination reduces mortality from cancer of the prostate.

Transrectal Ultrasonography

Transrectal ultrasonography (TRUS) does not qualify as a good screening tool for cancer of the prostate. In this test, the classic finding for cancer of the prostate is a hypoechoic area. The sensitivity and specificity of the examination are operator dependent, as is the definition of a suspicious area. Examiners whose definitions of suspicious findings are less stringent have higher biopsy rates and higher cancer detection rates. For example, Lee et al. reported a biopsy rate over 8% and a detection rate of prostate cancer of 2.5% (10). In contrast, Catalona et al. reported a biopsy rate of 100% and a detection rate of 24% (2). It is plausible that the high detection rate reported by Catalona et al. is explained by the high biopsy rate in a disease with a high prevalence in the general population (30% in men over 50 years old). Therefore, the high detection rate may be unrelated to the findings on transrectal sonography, serum PSA, or digital rectal examination.

In a study reported by Walsh et al., TRUS was performed on 59 patients who subsequently underwent radical prostatectomy (11). Specimens were step-sectioned, and histologic cancer of the prostate was mapped to correlate with the preoperative ultrasonographic and digital rectal examination findings. Of the 59 patients, 25 were found to have lateral malignancies not detected

by digital rectal examination. TRUS predicted prostate cancer in only 13 of these 25 patients; thus, the positive predictive value of TRUS was 52%. These data confirm the lack of efficacy of TRUS as a screening tool.

Prostate-Specific Antigen

Prostate-specific antigen (PSA) is a single-chain glycoprotein with a molecular weight of 33 kD. The molecule is a serine protease which belongs to the kallikrein family. PSA is produced by the ductal and acinar epithelial cells of the normal prostate gland. It is also secreted by prostate cancer cells. Normal prostate epithelial cells produce more PSA per cell than cancer of the prostate.

In 1971, PSA was first discovered in the seminal plasma (12). The concentration of PSA in seminal fluid is very high (10^6 μ cg/L). In the seminal fluid, PSA cleaves a protein produced by the seminal vesicles and is involved in the liquefaction of the seminal coagulum. In 1979, PSA was isolated from prostatic tissue (13). A year later, it was found to be elevated in serum from patients with cancer of the prostate (14).

PSA is present in serum in three molecular forms: (a) free PSA (molecular weight 33 kD); (b) PSA bound to the proteinase inhibitor α_1 -chymotrypsin (ACT) (molecular weight 100 kD); and (c) PSA bound to α_2 -macroglobulin (molecular weight 800 kD). Current commercial PSA immunoassays can measure only free PSA and PSA-ACT complex. In serum from normal men, the ratio of free PSA:PSA-ACT complex is approximately 1:4.

PSA is prostate specific but not cancer specific. Serum PSA values may be elevated in patients with prostatitis, prostatic infarct, postprostatic instrumentation and, more important, in patients with benign prostatic hyperplasia (BPH). Forty-three percent of patients with prostate cancer have PSA values under 4 ng/mL (normal range 0–4 ng/mL). Twenty-five percent of men with BPH have serum PSA values over 4 ng/mL. A serum PSA value over 4 ng/mL has a positive predictive value for diagnosing cancer of the prostate of 49%; a serum PSA level that is over 10 ng/mL has a positive predictive value of 75%. Given the large overlap in serum PSA values in men with BPH and men with prostate cancer whatever the cutoff level chosen, the usefulness of PSA as a screening tool for prostate cancer is questionable. Several modifications have been proposed to increase the value of PSA as a diagnostic tool in detecting cancer of the prostate.

PSA Density. Several investigators have studied the relationship between ultrasonographically determined prostate volume and serum PSA levels in patients with BPH and prostate cancer. An attempt was made to quantify this association so that it could be used to distinguish BPH from prostate cancer. The PSA density is defined as the serum PSA divided by prostate volume as determined ultrasonographically.

Babian et al. studied a select population of 103 patients who were referred to a urology service because of prostate abnormalities detected on physical or ultrasonographic examination. By analyzing prostate volumes, serum PSA values, and biopsy results, the researchers concluded that in patients with PSA values of 4.1–20 ng/mL, the prostate volume should be determined sonographically. If the prostate volume is 25 cm³ or less, the likelihood of cancer is greatly increased. In other words, a higher PSA density is associated with a higher likelihood of malignancy (15).

Benson et al. evaluated patients with serum PSA levels in the range of 4–10 ng/mL using PSA density. They recommended a PSA density cutoff point of 0.15 ng/mL as the test of optimal sensitivity and specificity for diagnosing prostate cancer (16).

With colleagues, I studied 75 men referred by their primary care physician for urologic evaluation because of symptoms of prostatism, abnormal digital rectal examination, or elevated serum PSA value. All patients underwent TRUS and prostatic needle biopsy under ultrasonographic guidance. In the group of patients with BPH, the range of serum PSA values was 9–32 ng/mL (mean, 8.6 ng/mL), and prostate volume ranged from 16 ccs to 190 ccs (mean, 66 ccs). Biopsy revealed BPH in 50 patients and prostate cancer in 25 patients. The serum PSA in biopsy-proven prostate cancer ranged from 3.7 ng/mL to 171.6 ng/mL (mean, 26.6 ng/mL). The range of prostate volumes in the patients with prostate cancer was 14–158 ccs (mean, 40 ccs). The PSA density in the group with BPH ranged from 0.03 to 0.9 (mean, 0.15), whereas the PSA density in the prostate cancer group ranged from 0.14 to 1.99 (mean, 0.66).

In the same study, three potential criteria for prostate biopsy were evaluated retrospectively based on ability to have predicted prostate cancer in the study patients: (a) serum PSA value over 4 ng/mL; (b) serum PSA value over 10 ng/mL; and (c) PSA density (PSAD) index over 0.15 (the mean PSA density in the BPH group). Of these three parameters, PSA density over 0.15 appeared to be

TABLE

Accuracy of Three Prostate-Specific Antigen (PSA) Criteria for Prostate Biopsy in Predicting Presence of Prostate Cancer

	Sensitivity	Specificity	Negative PV	Positive PV
PSA density	0.96	0.70	0.97	0.62
PSA > 4 ng/mL	0.96	0.34	0.94	0.42
PSA > 10 ng/mL	0.68	0.66	0.73	0.50

the most accurate in predicting prostate cancer on biopsy (Table).

Although PSA over 4 ng/mL was equally sensitive to PSA density (sensitivity, 0.96), PSA density was nearly twice as specific (0.70 vs. 0.34). Similarly, PSA over 10 proved to be nearly as specific as PSA density (0.66 vs. 0.70), but PSA density was 41% more sensitive. Although PSA density appears in these data to be a useful tool in diagnosing prostate cancer, the value of this measure has not been tested in the screening setting.

Age-Specific Serum PSA Measurements. Serum PSA increases with age. The possible etiologic factors in this age-related increase are increasing prostatic size, increase in the incidence of latent carcinoma of the prostate, and increased inflammation in prostates of larger size. In a community-based study involving healthy men 40–79 years of age who had no clinical evidence of prostate cancer, the PSA concentration was found to correlate with patient age (r , 0.43). The 95th percentile was chosen as the cutoff point to establish the upper limits of normal for age-adjusted serum PSA values. It was determined that the appropriate normal reference ranges for serum PSA values were 0–2.5 ng/mL (men aged 40–49 years), 0–3.5 ng/mL (men aged 50–59 years), 0–4.5 ng/mL (men aged 60–69 years), and 0–6.5 ng/mL (men aged 70–79 years) (17).

In a separate study, these age-specific reference ranges for serum PSA were applied to 2988 men aged 60 years or older who attended a single urologic practice. The age-adjusted PSA value (as compared to non-age-adjusted PSA) enhanced serum PSA specificity by 11% and positive predictive value by 5%. However, the sensitivity of the serum PSA value decreased by 9% using the age-adjusted ranges (18). It can be argued that, in an older population, enhanced specificity is desirable, even at the cost of reducing sensitivity, because greater specificity will reduce the number of invasive procedures in the population. The usefulness of age-specific PSA values in screening is currently unknown.

Free Serum PSA. Of the three major forms of serum PSA—free PSA, PSA α 1-antichymotrypsin, and PSA α 2-macroglobulin, only free PSA

and PSA-ACT are immunodetectable by current commercial assays. Several reports have indicated that patients with prostate cancer have a lower percentage of free PSA than do patients with BPH (19). In one study that evaluated 144 men with BPH and 121 men with prostate cancer, the median free PSA:total PSA ratio was 0.18 in the prostate cancer patients and 0.28 in men with BPH (20). Prostate cancer cells produce higher levels of ACT than do noncancerous prostate cells, which may explain the higher proportion of complexed PSA in the prostate cancer patients. Current studies are investigating the utility of these measurements of free vs. complexed PSA in screening for prostate cancer.

PSA Velocity. Serial measurements of PSA have been reported to improve the specificity of this test. In a retrospective analysis of sera stored as part of the Baltimore Longitudinal Study of Aging, an annual increase in serum PSA levels of 0.75 ng/mL or more distinguished prostate cancer patients from controls and patients with BPH (21).

The change in serum PSA with time has been termed "PSA velocity" (PSAV). Even though the physiologic variation in serum PSA levels may be as high as 30%, the PSAV may, in individual patients, give valuable information on the natural history of prostate cancer. However, before this test can have practical applications, studies must be carried out to determine the optimal sampling interval and follow-up time needed to utilize PSAV as a screening tool for prostate cancer. It is also possible that PSAV will pick up prostate cancers after they are no longer organ confined. Larger studies, with longer follow-up times, will help determine the utility of this measurement.

Conclusions

The routine use of serum PSA levels to screen for prostate cancer has led to an increase in reported cases, with a higher proportion of organ-confined cancers. However, early detection has not yet been demonstrated to decrease mortality from prostate cancer. Advocates of screening argue that the data are not yet available to show that PSA screening will not improve survival. Moreover, they state that it will require ten years or more before the reduction in mortality resulting from screening becomes apparent.

In the United States, only one of every five men diagnosed with prostate cancer will die from their disease. This implies that four out of five men with prostate cancer have less aggressive cancers, and early detection will increase the pro-

portion of these milder cases detected. Approximately 50% of patients undergoing radical prostatectomy will have disease spread beyond the confines of the prostate and are, therefore, not curable. This raises two key questions: (a) Is curative therapy necessary for the 80% of patients with less aggressive cancers? (b) Is curative therapy possible for the 20% of prostate cancer patients with more advanced disease? These questions become even more difficult to answer when considering individual patients and the particular ratio of risk to benefit of early screening and treatment in each case.

Not enough data are currently available to answer these questions. Critical prospective studies are currently under way in the United States and Europe to assess the benefit of screening for prostate cancer. In these studies, patients are randomized to screening or no-screening groups, and the effect on mortality determined. It is estimated that the study must continue for at least 15 years in order to obtain meaningful results.

From the scant data available on the natural history of cancer of the prostate and the efficacy of treatment of localized disease, two groups of men seem to derive the most benefit from screening in terms of reduction in mortality. The first group are men over age 50 with a positive family history of prostate cancer. The second group are men over age 50 with a life expectancy that is more than fifteen years. Even in these two groups, however, patients should be carefully informed of the risks and benefits of early screening and treatment of cancer of the prostate.

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Screening in the New Environment of Medicine:

Questions and Answers

Paul L. Gilbert: It sounds to me like the most important thing with regard to screening is informed advice for the patient, because knowledge is not yet quite clear-cut, and probably the knowledge base of the internist and his or her ability to offer informed advice is critical in deciding who gets tested and who does not.

Barry S. Collier: I have heard the suggestion that an alternative to the recommendations for colon cancer screening is a single colonoscopy at age 50 as the one and only screening test.

Itzkowitz: That alternative is being looked at fairly seriously now. In fact, some recommend a once-in-a-lifetime sigmoidoscopy at around age 55 or 60, with the realization that we may be missing some of the more proximal lesions. The issue of using colonoscopy as a screening device—whether it is used once or often—depends on manpower, cost, and the need for sedation, which may produce complications. It might not be unreasonable to do a colonoscopy once, maybe not at age 50 but at age 55 or 60. The issue is cost. If it were \$100 each, people might be more willing to accept that convention. There is a difference between screening and case finding. Strictly speaking, screening applies to a general population, people not otherwise motivated to come into a medical center—sending out Hemoccult cards to such a population amounts to screening. Case finding, however, concerns the person who, for some reason, shows up at the office and has a reason to be there—family history, symptoms, whatever. The question I am often asked, “If it was your mother, what would you do?” is a question about case finding, not about screening. When somebody asks me that question, I say, “I would like my mother to have a colonoscopy, so that I can be really certain.” But I think the issue is going to turn on economics more than anything else.

Question: Leaving economics out, is that a medically sound alternative?

Itzkowitz: Can you clear a patient's colon as free of disease once and then just forget about that

potential problem? That is a sound alternative. Doing a single exam for patients aged 50 may be a problem, because a lot of those exams may be negative. The trick is trying to find the optimal age for detecting the most lesions. I think a screening colonoscopy at age 60 may be prudent, because if an adenoma is removed, or even if a cancer is found and the patient goes to surgery, the chances of the patient going on and developing further adenomas and cancers that are significant and are going to impact on survival are small.

Gilbert: In the October 28, 1993 issue of the *New England Journal of Medicine* (vol. 329, pp 1351–1354), some half-dozen letters attacked the Minnesota study Dr. Itzkowitz cites, and another half-dozen defended it. Among the economic studies discussed in the letters, one suggested that what he wants to do would cost over \$6 billion a year, and another compared it in effectiveness and cost to breast cancer screening in women. Those letters were probably more valuable than the entire journal.

Question: A technical question about the two windows in the fecal occult blood test for colon cancer: is the patient supposed to use the same dipstick and smear the same thing on both windows, or is each window supposed to get a separate dip and a separate specimen?

Itzkowitz: That hasn't been addressed in a formal study, but it is probably better to advise patients to apply separate stool specimens to each window, and do it for three consecutive bowel movements. Some recommend doing it on three consecutive days, but if someone has three bowel movements in one day, it is OK to do it all in one day and submit that.

Collier: What are the risks of the prostatic biopsy?

Kirschenbaum: It is an invasive procedure producing mild to moderate discomfort. There is a small risk, less than 1%, of bleeding and infection. There is a 10%-20% risk of picking up latent carcinoma of the prostate and subjecting the pa-

tients to unwarranted anxiety and possibly unnecessary treatment.

Question: Does the digital rectal examination have any effect on PSA levels? If so, should the PSA be done first?

Kirschenbaum: The data seem to indicate that gentle rectal examination has no effect on serum PSA.

Question: The treatment of prostate cancer is still a huge problem. Doesn't that make the whole screening issue even more questionable in terms of therapy?

Kirschbaum: The answer to your question is yes. I think that any patient whose life expectancy is at least 15 years should consider screening and treatment. Do I have solid data for that? No. But the data are more solid on the other extreme: a patient aged 70 or more with life expectancy less than 10 years probably should be advised against screening.

Question: Maybe this is the wrong question to

ask a urologist, but how about radiation as a form of therapy once the disease is picked up?

Kirschenbaum: The controversy over the relative effectiveness of surgery and radiotherapy for treatment of localized cancer of the prostate is not resolved. My bias as a urologist is that surgery is more effective than radiotherapy.

Question: What are the complications of surgery and of radiotherapy?

Kirschenbaum: They have different complications.

Gilbert: A survey published in one of the medical journals in England surveyed a group of people who were treated for prostate cancer. As a group, the radiologists would have opted for radiation for themselves, and the urologists for surgery for themselves. As an internist, I am impressed by how well patients who have prostate cancer do under both circumstances. It is remarkable how quickly after radical prostatectomy patients leave the hospital, if they do not develop thrombophlebitis, of which there is a high incidence.

The Three Mechanisms for Coronary Artery Disease Progression:

Insights into Future Management

MARY ANN McLAUGHLIN, M.D., AND VALENTIN FUSTER, M.D., PH.D.

Abstract

The basic mechanisms of atherosclerotic progression have been well elucidated during the last few years. Basic experimental and clinical information has helped define the three stages of progression. In this review we outline the pathologic and clinical differences between slow, rapid, and intermediate progression. The eight morphologically different lesions (types I, II, III, IV, Va, Vb, Vc, and VI) in their various stages are defined. The relationship between specific type of lesion and chronic endothelial injury, cardiac risk factors, and increased vascular permeability to lipids is noteworthy.

In regard to the acute coronary syndromes, the fate of plaque rupture and our understanding of "passive" vs. "active" rupture are defined. In addition to the phenomenon of plaque rupture, the thrombogenicity of atherosclerotic plaques in the genesis of coronary syndromes is described. The combination of plaque disruption and a high thrombogenic risk profile—including local and systemic factors—is vital to understanding the genesis of the acute coronary syndromes.

In approaching the use of these new insights to arrest or reverse the atherosclerotic process, it is essential to remember that the disease process starts early in life and takes many years to progress to the symptomatic stage. The future holds promise for the development of preventive strategies to halt the progression of coronary disease—the number one killer in the United States.

THE PROGRESSION OF ATHEROSCLEROSIS is complex. Normal aging of arteries includes intimal thickening, loss of elasticity, increase in calcium content, and increase in diameter. The World Health Organization has defined atherosclerosis as a "variable combination of changes of the intima of arteries, consisting of the focal accumulation of lipids, complex carbohydrates, blood and blood products, fibrous tissue and calcium deposits, and

associated with medial changes" (1). Significant advances in our understanding of this phenomenon have been made in the last three decades, but this paper focuses on those of the past few years.

The Five Phases of Coronary Atherosclerosis

In 1992, five distinct phases of coronary atherosclerosis were defined (Fig. 1) (2):

- Phase 1: presence of the early, slowly progressing atherosclerotic plaque that occurs in everyone younger than 25 years old
- Phase 2: development of plaque with a high content of fat that is friable and apt to rupture
- Phase 3: plaque ruptures, leading to formation

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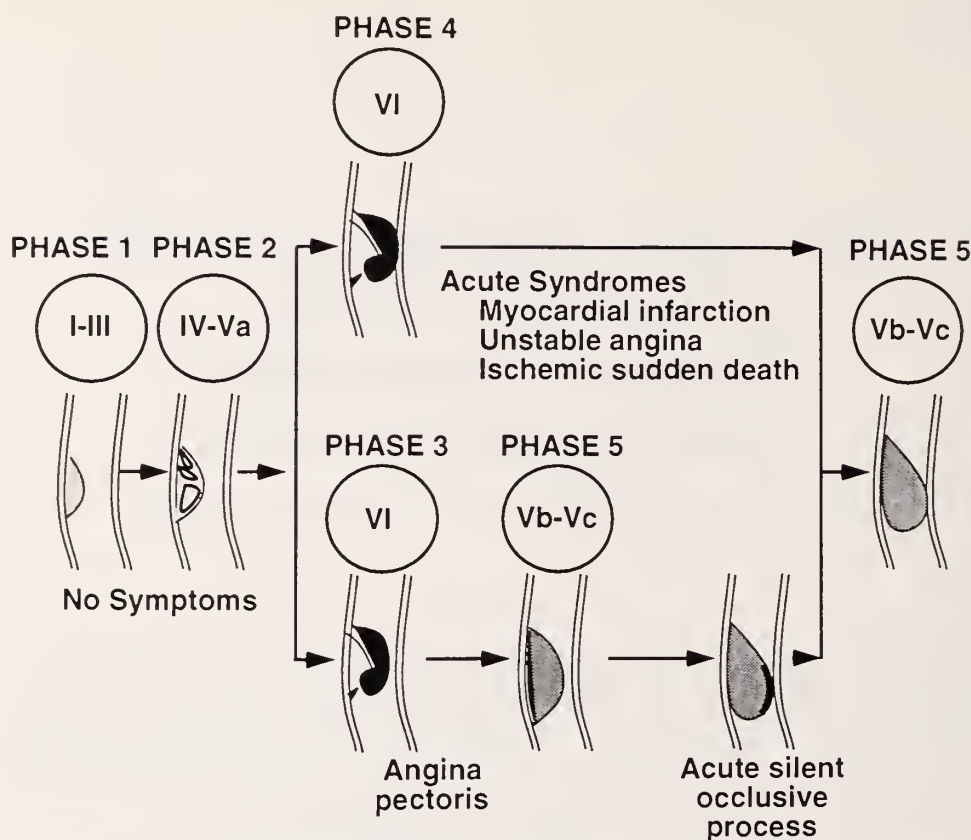


Fig. 1. Staging (phases and lesion morphology) of progression of coronary atherosclerosis by gross pathologic and clinical findings. Modified from V. Fuster et al., *N Engl J Med* 1992; 326:244, with permission.

of a mural thrombus organized by connective tissue and a subsequent increase in stenosis and possible angina. Rupture of the plaque is probably one of the main mechanisms by which the atherosclerotic process advances

- Phase 4: fatty plaque breaks, and the ensuing thrombus is no longer mural but completely occlusive, leading to an acute coronary syndrome such as myocardial infarction, unstable angina, or ischemic sudden death
- Phase 5: development of a severely stenotic and fibrotic plaque, which, by stasis or de-endothelialization, can ultimately become totally occlusive due to a thrombus or a rapid myoproliferative response

About two thirds of coronary occlusions result from the late stenotic plaques of phase 5 and are not related to plaque disruption. Although the rupture of less stenotic, lipid-rich plaques can lead to occlusion and subsequent infarction or other acute coronary syndromes, the process of occlusion from late stenotic plaques tends to be silent because the preceding severe stenosis and ischemia enhance protective collateral circulation (2, 3).

Three Mechanisms of Atherosclerotic Progression

Early Slow Disease Progression

Three mechanisms of atherosclerotic progression exist (Fig. 2) (4). Over the last few years, basic experimental and clinical information has elucidated the basic mechanism of such progression. The early slow progression of disease involves progression of lesion types I, II, and III into types IV and Va (Fig. 2). Type I lesions, which are not grossly visible, contain isolated macrophages with oxidized lipid droplets, which are defined as foam cells. Type II lesions, which are identified as fatty streaks on Sudan staining, contain significant intracellular lipid droplets in foam cells and smooth muscle cells. Type III lesions appear on Sudan staining as raised fatty streaks and contain many small extracellular lipid cores as well as lipid droplets in foam cells and in an increasing number of smooth muscle cells. These three types of lesions relate to the original phase I of Fuster's classification (Fig. 1). If the influx of lipids and accumulation into the vessel wall continues and is more significant than the efflux, the process evolves with a continuous slow progression of

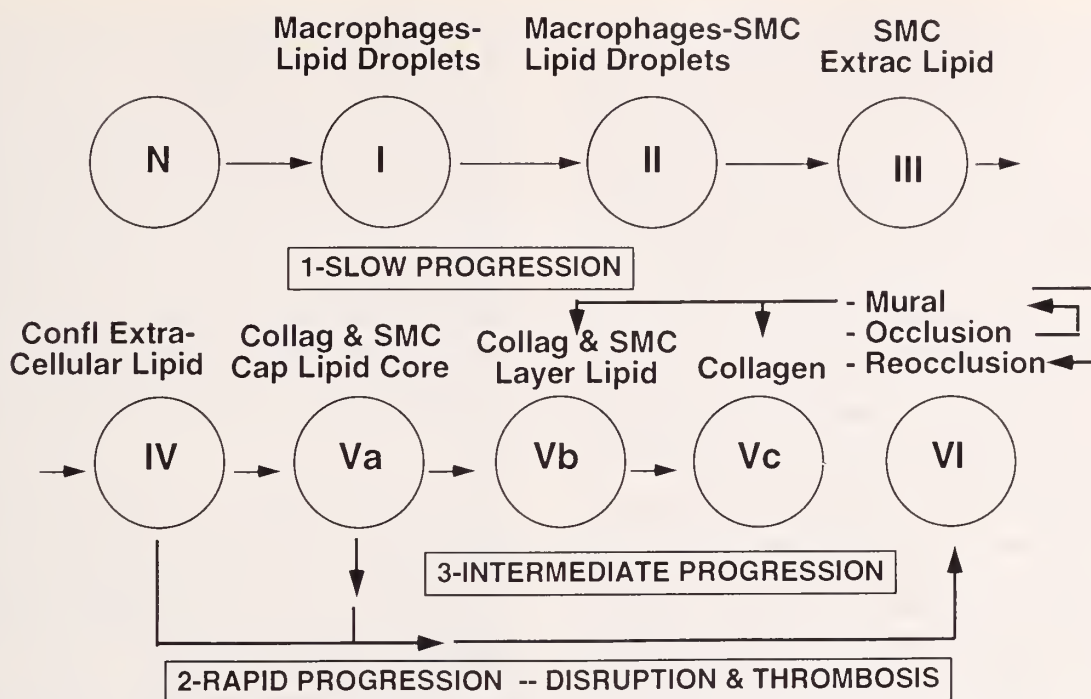


Fig. 2. Lesion morphology in progression of coronary atherosclerosis by histopathologic findings. SMC, smooth muscle cells. *Modified from V. Fuster, Circulation 1994; 90:2127, with permission.*

these lesions into types IV and Va. The type IV lesion contains a predominance of extracellular lipid, mainly diffuse, whereas the type Va lesion has a high lipid content, mainly localized, and a thin capsule.

It has been proposed that lesions of types I, II, and III evolve as a result of chronic endothelial injury, the presence of cardiac risk factors, and increased vascular permeability to lipids and monocyte-macrophages (4).

Endothelial Injury. Endothelial injury can be classified by stage of increasing severity (5):

- Type I: functional and morphological alterations of endothelial cells, as occurs in the initial stage of atherosclerosis.
- Type II: endothelial denudation, as may occur in relatively earlier stages of atherosclerosis or in the latest stages when plaques are very stenotic
- Type III: endothelial denudation with damage to the intima and the media, as occurs in plaque fissuring and rupture in later stages of atherosclerosis (5).

Spontaneous atherosclerotic lesions tend to develop in certain regions of the circulation, despite exposure to the same lipoprotein concentrations throughout the circulation. It is believed that variations in local hemodynamics explain this phenomenon. For example, atherogenesis is likely to occur at regions of low shear stress with

complex secondary flow patterns, areas of standing recirculation, and bend points and bifurcations, where oscillatory hemodynamic changes occur (6–8). In these regions, the endothelial cells undergo morphologic changes in response to changes in shear stress, which may alter endothelial permeability to certain molecules (type I injury). In addition, stagnation of blood flow may permit increased uptake of atherogenic particles as a result of prolonged contact with endothelium (9, 10). Metabolically, the endothelium expresses on its surface specific adhesive glycoproteins that attract circulating monocytes and loses its capability to synthesize vasodilating molecules such as prostacyclin, nitric oxide, or EDRF. Hypercholesterolemia and other systemic risk factors increase the morphologic or functional endothelial dysfunction, but not necessarily early endothelial denudation.

Other coronary risk factors also promote this phenomenon of damage in the early stages of disease. For example, hypertension enhances local shear factors. In addition, advanced glycosylated end products in diabetes, chemical irritants in tobacco smoke, circulating vasoactive amines, may all lead to type I chronic endothelial injury, favoring the influx of lipids into the intima (2, 5).

Lipid Entry into the Arterial Wall. The lipids that are deposited in the atherosclerotic lesions are mostly derived from plasma low-density lipoprotein (LDL) (2). A specific LDL receptor in

the liver is responsible for the metabolism and elimination of plasma cholesterol (11). Since the number of these receptors seems to be genetically determined, this reduction explains the presence of hypercholesterolemia in some patients with a strong family history of coronary artery disease. The internalization and intravascular accumulation of cholesterol and its esters depends on both active and passive mechanisms.

There are a probable five processes in the early stage of the disease (Fig. 3).

The first and most important factor is shear stress, or turbulence of blood flow. Also, coronary risk factors promote dysfunction of the endothelium in the early stages of disease.

In stage 2, LDL recognizes this dysfunctional endothelial layer, in the low shear regions, where there is high residence time. The intravascular accumulation of cholesterol depends on two mechanisms: (a) receptor-dependent active transport (specific receptors are located in the endothelial cell and in other cells within the vessel wall (12); and (b) receptor-independent passive transport, which presumably occurs when endothelial dam-

age is more severe (2). After entering the vessel wall, the LDL is oxidized (13).

In stage 3, this oxidized LDL triggers the synthesis in the endothelium of adhesive molecules, including MCP1 and MCSF, which attract the monocytes to enter the vessel wall (14). Monocytes and macrophages take up LDL via the LDL receptor without formation of cholesterol deposits, but oxidized LDL is taken up much more rapidly via the scavenger receptor (acetyl-LDL) (15). Excessive intracellular accumulation of lipoprotein may occur, since the macrophage receptors for modified LDL are not regulated. These macrophages which uptake fat are converted to foam cells.

In stage 4, if there is an excess of foam cells, presumably the HDL circulating in blood takes up the excess oxidized LDL. If, however, entry of LDL exceeds its exit, the foam cells with a high content of oxidized LDL will break and release oxidized LDL and free radicals.

In stage 5, these toxic products can damage the endothelium further, leading to type II injury with endothelial denudation.

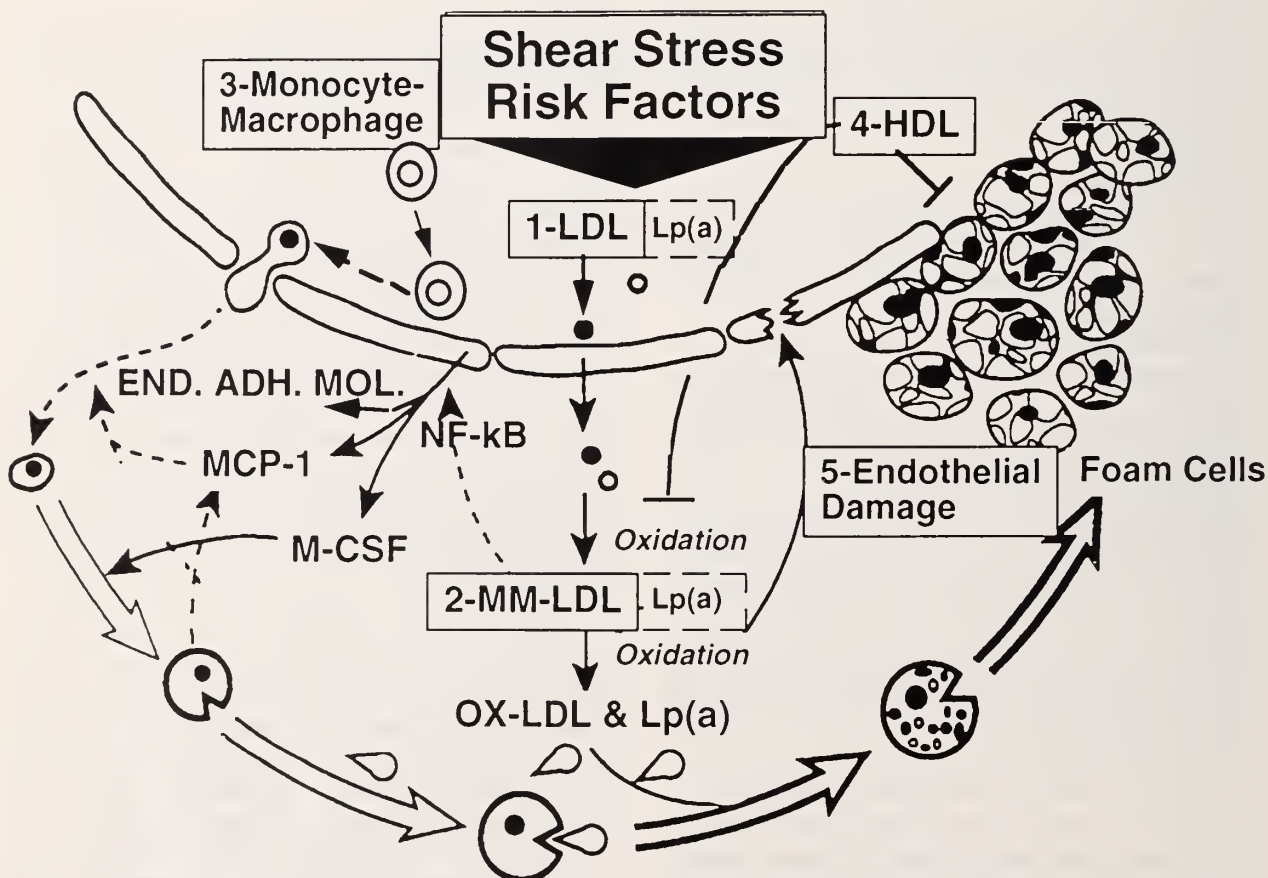


Fig. 3. Pathogenesis of phase I of progression: chronic endothelial injury and risk factors—influx, accumulation, and fate of lipids and monocyte-macrophages. LDL, low-density lipoprotein; HDL, high-density lipoprotein; Lp(a), lipoprotein(a); OX, oxidized; END.ADH.MOL., endothelium adhesion molecule; MCP-1, monocyte chemotactic protein-1; M-CSF, monocyte-colony stimulating factor; and MM, minimally modified. Modified from D. Steinberg, *Circulation* 1991; 86:1420, with permission.

Monocyte-Macrophage Recruitment into the Arterial Wall. The initial events in atherogenesis include monocyte adherence as a result of the expression of adhesive endothelial surface glycoproteins, such as VCAM-1 (athero-ELAM), and others. Oxidized LDL and shear stress have been found to regulate the expression of both VCAM-1 and ICAM-1 (16). In advanced stages of the disease, the macrophage is involved in the formation of foam cells and the lipid core. Macrophages may act as antigen-presenting cells to T-lymphocytes, as scavenger cells to remove noxious materials, and as sources of growth-regulatory molecules and cytokines.

Later in the process, several specific molecules may be relevant in attracting and modifying monocytes within the subendothelial space. These molecules include chemotactic protein (monocyte chemotactic protein-1, or MCP-1) synthesized by vascular cells (17), colony-stimulating factors (CSFs), and transforming growth factor (TGF β) (18). In more advanced stages, during which there is significant connective tissue production and tissue necrosis, the more predominant macrophages infiltrate the site of the ruptured plaque.

Rapid Disease Progression

Rapid progression of disease involves the progression of lesions of type IV and Va to lesion type VI (Figs. 1, 2). In atherogenesis, lipid accumulation, cell proliferation, and extracellular matrix synthesis may be expected to be linear with time. However, as is known from angiographic studies, the progression of coronary artery disease is neither linear nor predictable (19). Small plaque rupture or fissure and subsequent mural thrombosis are frequent and play an important role in both silent and symptomatic progression of atherosclerosis (20). It has become apparent that arteriographically mild coronary lesions may be associated with significant progression to severe stenosis or total occlusion, and these lesions may account for up to two-thirds of the patients in whom unstable angina or other acute coronary syndromes develop.

Angiography cannot accurately predict the site of future coronary occlusion, but it is probable that the more severe the coronary disease is at angiography, the higher the likelihood of the presence of small plaques prone to disruption (19). It may soon be possible to detect fatty plaques within the vascular system by high-resolution noninvasive biochemical imaging techniques.

In an autopsy study of coronary arteries in patients who died of noncardiac events, Davies et al. (20) found that 17% of patients had fissures in atherosclerotic plaques, as well as overlying thrombi in some cases. Fissuring and healing, therefore, may contribute to the evolution of early lesions to more advanced stages. In fact, pathologic studies of patients who died from ischemic heart disease showed a morphology of previously healed fissures with various stages of thrombosis and thrombus organization. Most fissures probably reseal and incorporate thrombus at the same time, but do not produce clinical syndromes (20). Falk also found layered thrombi overlying fissured plaques in patients who died of unstable angina or died suddenly (21). This finding suggests that recurrent episodes of mural thrombosis lead to gradual vascular stenosis and, eventually, occlusion. In addition, thrombus formation can occur not only at sites of rupture of relatively small "lipid-rich" plaques, as part of the second mechanism of progression, but also at sites of severely stenotic "fibrotic" plaques that are de-endothelialized, as part of the third or intermediate mechanism of progression.

Plaque Rupture. Lesion types I, II, and III are differentiated by their proportion of lipids, macrophages, and smooth muscle cells, and by whether the lipid is intracellular or extracellular. The advanced lesions containing a predominance of extracellular lipids are type IV lesions. Type Va lesions contain a dense accumulation of extracellular lipids within a defined region of the intima, separated from the vascular lumen by a thin fibrous cap. This lipid core is defined by the extracellular lipid accumulation. Plaques that undergo disruption tend to be relatively soft and have a high concentration of cholesterol esters, rather than of free cholesterol monohydrate crystals.

If the strain of the fibrous cap components exceeds the deformability, the fibrous cap may rupture (8). If the lipid core components are exposed to blood, thrombus formation may occur, resulting in a type VI or complicated lesion (4). Marked oscillations in shear stress or acute changes in coronary pressure or tone may contribute to plaque rupture. However, plaque rupture does not always occur at regions of high stress, suggesting that variations in the material properties of plaque also contribute to plaque rupture (22). Plaques that rupture usually contain less collagen and have less tensile stress than do intact plaques (23). Computer modeling analysis of tensile stress across the vessel wall reveals high concentrations of stress at the ends of plaque caps

overlying a lipid pool. If the extracellular lipid pool exceeds 45% of the vessel wall circumference, the plaque cap lacks underlying collagen support and is more susceptible to rupture (24).

In addition to the relatively "passive" phenomenon of plaque rupture, a better understanding of "active" rupture related to macrophage activity is evolving. Recently, atherectomy specimens obtained from patients with acute coronary syndromes, including a high proportion of patients with unstable angina, revealed significantly more macrophage-rich areas than did specimens from patients with unstable angina (25). These and similar observations at autopsy suggest that macrophages and, to a lesser degree, T lymphocytes are markers of unstable atherosclerotic plaques and may play a significant role in the pathophysiology of unstable angina and other acute coronary syndromes (24, 26, 27).

Within this context, it is known that macrophages can release metalloproteinases such as interstitial collagenase, gelatinase, and stromelysin, which have been identified in atherosclerotic plaques (28, 29). Recently, an increase in collagen breakdown was documented when monocyte-derived macrophages were incubated with human aortic plaques, indicating that macrophages could be responsible for an "active" phenomenon of plaque disruption (30). Also, recent studies support the fact that mast cells may play a role in triggering matrix degradation and an ensuing rupture of coronary plaques (31).

Thrombogenicity of Atherosclerotic Plaques.

The contribution of change in plaque geometry and thrombosis to progression: Disruption of a vulnerable or unstable plaque, with a subsequent change in plaque geometry and thrombosis, results in a type VI or complicated lesion (4). Histopathologically, plaque fissuring comes in various shapes and sizes. The tears may be small and may allow blood to enter and expand the plaque but may not result in thrombus formation in the arterial lumen, or may only result in a mural thrombus that, in being organized by connective tissues, contributes to the rapid progression of the disease. The tear may be large, and the thrombus formed within the lumen may occlude the vessel. Such a thrombus may be partially lysed or be replaced in the process of organization by the ubiquitous vascular repair response, also contributing to the rapid progression of the disease.

The role of thrombus incorporation in plaque progression has been outlined by Bini et al. (32) and Smith et al. (33), who used antibodies directed to platelets, fibrin, fibrinogen, and degradation products. In advanced and fibrous plaques,

products related to platelets and fibrin were detected in the intima, neointima, and medial layer, especially in areas of loose connective tissue. Also, recent studies using in situ hybridization of atherosclerotic plaques obtained at endarterectomy and during angioplasty suggest that thrombus formation or organization and acute or subacute growth of atherosclerotic plaques commonly occur together (34).

Pathogenesis of thrombosis: The initiation of thrombus formation is mainly dependent on the different atherosclerotic components exposed at different degrees of plaque injury. Superficial plaque injury with exposure of macrophage-rich or collagen-rich matrix, which might be present in small plaque fissures, is associated with less platelet deposition than that seen after deep injury with exposure of the lipid-rich core of the plaque. The lipid core, or most thrombogenic component of the plaque, is approximately six-fold more thrombogenic than the collagen-rich component (35). Therefore, the atheromatous plaques with lipid-rich "gruel" are not only the most likely to rupture but are also the most thrombogenic. Tissue factor protein has been identified immunohistochemically in a scattered pattern within the atheromatous core of human carotid plaques (34, 36), and its role in activating the coagulation cascade after plaque rupture is now being investigated by our group and others.

Thrombus pathophysiology: In addition to describing the process of plaque disruption and thrombus development at the site of plaque disruption, it is important to examine the local and systemic factors that occur at the time of coronary plaque disruption that may influence the amount and duration of thrombus deposition and thus the clinical implications. Most ruptured plaques re-seal by small mural thrombi, and the organization of thrombi leads to silent growth of the lesion. When the thrombi are large, they can impair coronary blood flow, leading to the acute coronary syndromes (2, 4). Several local and systemic factors may influence whether a thrombus remains at an intermediate stage as a mural, nonocclusive, clinically silent thrombus or proceeds rapidly to an occlusive thrombus.

Local Factors: Degree of plaque disruption. The degree of disruption is important in thrombosis. Our group has shown that exposure of sub-endothelial layers to blood flowing at a high shear rate results in platelet adhesion and aggregation. In these experiments, the resulting thrombus is labile, may be partially dislodged from the substrate by the flowing blood, and leaves a small

residual thrombus (37). If deeper vascular layers are exposed to flowing blood in a similar manner, a dense, not easily dislodged platelet thrombus may appear. Clinically, if the surface of a coronary plaque is disrupted, a small mural thrombus may develop, probably leading to subsequent thrombus organization and asymptomatic growth of the lesion. Patients with unstable angina and acute myocardial infarctions experience a greater degree of plaque damage, leading to greater thrombotic coronary occlusion (2). In addition, fibrous cap disruption produces a rough surface within the arterial lumen that further stimulates the development of acute thrombosis. Perfusion studies performed on ex-vivo human aortic atherosclerotic plaques have shown that the roughness of the exposed surface, measured by the presence of flaps, dissections, fissures, and surface irregularities, influences thrombogenicity (35).

Local Factors: Sudden geometry change and degree of stenosis. The acute thrombotic response depends on the degree of coronary stenosis and sudden geometric changes following plaque rupture (4). High shear rates at the site of a significant stenosis predispose the artery to increased platelet and fibrinogen deposition by forcing both to the periphery (37, 38). A vessel with a small geometric change or mild stenosis may result in small mural thrombus; a larger geometric change or severe stenosis may result in a transient or persistent thrombotic occlusion, causing an acute coronary syndrome.

Local Factors: Residual thrombus. A residual thrombus is one of the most thrombogenic surfaces for several reasons. First, the residual thrombus encroaches on the vessel lumen, resulting in increased stenosis and high shear rate. Also, experimental observations indicate that thrombus is highly thrombogenic, since with spontaneous or therapeutic thrombolysis, thrombin bound to fibrin is exposed to the circulating blood, thus leading to further platelet and clotting activation (39–41).

Local Factors: Coronary vasoconstriction. Coronary vasoconstriction also alters the balance between myocardial oxygen supply and demand during acute coronary syndromes. In addition, because of the transient increase in stenosis, thrombogenicity may be enhanced if vasoconstriction occurs at the time of plaque rupture. Indeed, Maseri et al. first demonstrated spontaneous coronary vasospasm by angiography in patients with unstable angina (42). During acute coronary syndromes, there seems to be a predisposition for platelet-dependent (mediated by serotonin and thromboxane A₂) and thrombin-dependent vaso-

constriction (43, 44) at the site of plaque rupture. Recent data obtained in patients undergoing percutaneous angioplasty support the angiographic observation that transient vasoconstriction accompanies plaque disruption and thrombosis in the acute coronary syndromes.

Systemic Factors: Systemic factors may induce a primary hypercoagulable or thrombogenic state and may be responsible for formation of a large thrombus after plaque disruption. Catecholamines may induce platelet activation and thrombin generation (45–47). Catecholamines also enhance vasoconstriction and increase heart rate, possibly triggering plaque disruption. These effects of catecholamines may explain the development of infarction during emotional states, cigarette smoking, and cocaine abuse. That is, the coincidence of plaque rupture and a high catecholamine state may be highly thrombogenic. Hypercholesterolemia has been associated with hypercoagulability and enhanced platelet reactivity at the site of experimentally induced acute vascular damage (48). Lp(a) is an important risk factor for coronary artery disease and consists of Apo(a), a glycoprotein sharing structural homology with plasminogen, which may predispose patients to acute thrombotic complications (49). It has also been suggested that high-density lipoprotein (HDL) may participate in preventing intracoronary thrombus formation. HDL may stabilize PGI₂ through the function of Apo-A1.

Hemostatic proteins, fibrinogen, and factor VII have also been implicated as major thrombogenic risk factors. Multiple studies have shown that a high plasma fibrinogen level is an independent risk factor for coronary artery disease, particularly myocardial infarction (50–52). The largest study suggested that the relationship between fibrinogen level and extent of coronary disease is due mainly to a luminal occlusion. These data strengthen the fact that high fibrinogen levels are thrombogenic. The direct, independent, and statistically significant association between fibrinogen level and subsequent incidence of ischemic heart disease is as strong as the relation between cholesterol and ischemic heart disease (53). In addition to contributing to coronary artery changes, high fibrinogen levels influence blood and plasma viscosity and platelet aggregability. Fibrin strands provide a scaffold along which smooth muscle cells migrate and proliferate, bind thrombin, and produce mitogenic fibrin degradation products, which are mitogenic (54).

Several attempts to reduce fibrinogen levels have been reported in the literature. Smoking cessation is the most effective, weight and stress

reduction have an effect, and recently oral fibrates have been reported to be effective, but further trials are necessary (55). Recently it has been shown that in patients with coronary disease, enhanced thrombin-induced platelet aggregation is a marker for subsequent acute coronary events and disease progression (56).

Intermediate-Speed Disease Progression

Intermediate progression of atherosclerosis proceeds over a period of months. After plaque rupture and thrombus formation and organization, the highly stenotic lesions of type Vb and Vc evolve (Fig. 2). A process of de-endothelialization of the plaque surface occurs as a result of stenosis-related shear forces, and a process of repair also ensues.

Preliminary studies in the porcine model by our group employing staining for de-endothelialization reveal that progressive intimal proliferation occurs until the endothelium covers the surface. Platelet uptake, platelet adhesion, and probably growth factor released by platelets stimulate the intimal proliferation that occurs on the de-endothelialized surface. Therefore, it is conceivable in humans that, in the presence of a de-endothelialized stenotic lesion, the constant expression of platelet-derived growth factor may also lead to progression of smooth muscle cell proliferation and extracellular matrix formation. Eventually, this intermediate progression of disease results in further stenosis toward occlusion, associated or not at the end stage with thrombus formation. Indeed, such late occlusions resulting not from plaque ruptures but from highly stenotic lesions are frequent and mostly asymptomatic because of the protection by collaterals that have developed over time (3).

Integrated Pathogenesis of the Coronary Syndromes

A summary of current views on the pathophysiology of the various coronary syndromes is in order (2).

Patients with stable coronary artery disease commonly experience angina or silent ischemia when increases in myocardial oxygen demand outstrip the ability of stenosed coronary arteries to increase delivery. In contrast, unstable angina or ischemia, non-Q-wave myocardial infarction, and Q-wave infarction (on occasion these syndromes may be silent) present a continuum of the disease process and are usually characterized by an abrupt reduction in coronary flow.

In unstable angina, a relatively small fissuring or disruption of an atherosclerotic plaque may lead to an acute change in plaque rupture and a reduction in coronary blood flow, resulting in exacerbation of angina. Transient episodes of thrombotic vessel occlusion at the site of plaque rupture may occur, leading to angina at rest. The thrombus is usually labile, resulting in temporary (10–20 min) vascular occlusion. Also, the release of vasoactive substances by platelets, as well as vasoconstriction secondary to endothelial vasodilator dysfunction, may contribute to reduction in coronary flow. It has recently been suggested that in a subset of patients with unstable angina, an accelerated type of intimal hyperplasia may lead to partial obstruction and unstable angina without underlying evidence of plaque disruption and thrombosis (57). Overall, alterations in perfusion and myocardial oxygen supply probably account for two-thirds of the episodes of unstable angina, the remainder being caused by transient increases in oxygen demand (58, 59).

Non-Q-wave infarctions, caused by more severe plaque ruptures, result in more persistent thrombotic occlusion, lasting up to one hour (60, 61). An estimated fourth of patients with non-Q-wave infarctions may have an infarct-related vessel occluded for more than one hour, but the distal myocardial territory is protected by collaterals (61). Also, resolution of vasoconstriction may be pathogenically important in non-Q-wave infarction.

In summary, spontaneous thrombolysis, presence of collateral circulation, or resolution of vasoconstriction are important in preventing the development of a Q-wave infarction (2).

Larger plaque fissures may result in the formation of a fixed and persistent thrombus and subsequent Q-wave myocardial infarctions. Myocardial perfusion interrupted for more than an hour results in transmural necrosis of the involved myocardium. The coronary lesion responsible for the infarction is frequently only mildly to moderately stenotic, suggesting that plaque rupture with superimposed thrombus, rather than severity of the underlying lesion, is the primary determinant of acute occlusion (62, 63). In perhaps one-fourth of patients, coronary thrombosis results from superficial de-endothelialization or blood stasis in areas of high-grade stenosis. Here, the infarction may be small or not clinically evident. Finally, it is unclear if myocardial infarction may occur solely as a primary alteration of hemostatic risk factors, such as deficient fibrinolytic mechanisms, increased platelet aggregability, and activation of the coagulation system, independent of plaque disruption.

Conclusions

Recent research has yielded insight into the pathophysiology of atherosclerosis progression. In approaching the concept of arresting or reversing the atherosclerotic process, it is essential to remember that the process starts early in life and takes many years to progress to the symptomatic stage. The future holds promise for the development of preventive strategies to halt the progression of coronary disease—the number one killer in the United States.

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Evolving Concepts in the Pathogenesis and Treatment of Arterial Thrombosis

JAMES H. CHESEBRO, M.D., VINCENZO TOSCHI, M.D., MADDELINA LETTINO, M.D., RICHARD GALLO, M.D.,
JUAN J. BADIMON, PhD, JOHN T. FALLON, M.D., PhD, AND VALENTIN FUSTER, M.D., PhD

PLAQUE DISRUPTION WITH ACUTE THROMBOSIS is the major cause of acute coronary syndromes (1, 2). Thrombosis with platelet deposition and fibrin formation begins immediately (maximum within one to 24 hours) after injury, is usually mural and subocclusive, is influenced by local arterial wall substrates and by plaque geometry and the resultant rheologic alterations of blood flow, and is modified by systemic factors. Mild injury (defined as endothelial denudation) results in only a single layer of platelet deposition without macroscopic thrombus. Deep arterial injury through the internal elastic lamina into the arterial media, adventitia, or intimal plaque consistently causes a macroscopic, subocclusive platelet-rich thrombus over the area of injury (Fig. 1). Growth of thrombus can now be measured by monitoring minute-to-minute changes utilizing platelets labeled with indium 111 or technetium 99m and fibrinogen labeled with iodine 125.

Role of Thrombin

Thrombin appears pivotal for *in vivo* formation, growth, maintenance, consolidation, and dissolution of thrombus. It is also important for cellular proliferation after deep arterial injury, which leads to a greater proliferative response than does mild injury, a phenomenon apparently related to the amount of thrombus formed.

Thrombin is generated by activator complexes on phospholipid (including cell membranes) surfaces, and is evident in the arterial tunica media after injury (3, 4). Only minute amounts of thrombin are necessary to activate platelets which release a multitude of growth factors (3, 5). Thrombin also converts fibrinogen to fibrin and cross-links fibrin, which stabilizes the thrombus. Thrombin begets thrombin by activating coagulation factors more proximal in the cascade, directly by inducing tissue factor and indirectly by releasing growth factors that also induce tissue factor (Fig. 2) (1–3).

Formation of Thrombus. The factor or substrate that is the primary cause of arterial thrombosis is unknown but probably involves tissue factor, which is present in normal adventitia and atherosclerotic plaque and variably in tunica media and is inducible in smooth muscle cells and macrophage (1). This may partly explain the experimental observation (by immunohistochemical staining and by blood level of hirudin—specific thrombin inhibitor—required to prevent thrombus) of thrombin generation that is more extensive after deep than after mild arterial injury (Fig. 3) (3). Specific platelet activating receptor inhibitors and specific coagulation factor inhibitors have documented mechanisms of *in vivo* arterial thrombosis. Specific receptor inhibitors to thromboxane A₂ and serotonin do not prevent *in vivo* arterial thrombosis, but hirudin, the specific thrombin inhibitor, totally blocks formation of intraluminal mural thrombus after deep arterial injury (3, 6, 7). This documents the pivotal *in vivo* role of thrombin in thrombus formation (platelet and fibrin deposition). Blocking thrombin generation (Fig. 4) with warfarin by inhibiting vitamin K-dependent coagulation factors (prothrombin, factor VII, IX, and X) to $\leq 12\%$

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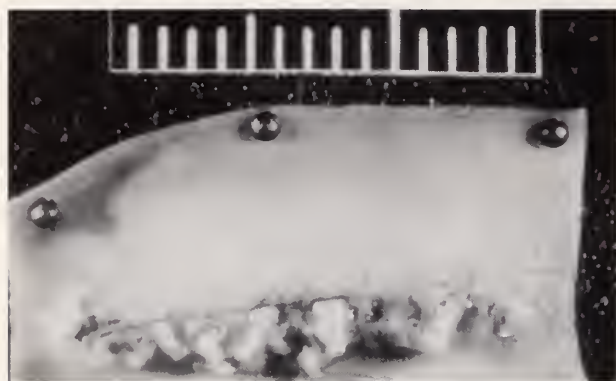


Fig. 1. Balloon injury of a porcine carotid artery results in diffuse endothelial denudation, which stains positive with Evan's blue dye, and a focal tear through the internal elastic lamina into arterial media, which is covered by a platelet-rich mural thrombus that tracks longitudinally over the tear and is typically subocclusive. Only approximately 5% lead to acute total occlusion.

of normal levels also totally prevents mural thrombosis after deep injury of porcine carotid and coronary arteries after angioplasty (8). Specific inhibition of factor X_a with tick anticoagulant peptide (TAP) also totally blocks thrombus formation after deep arterial injury in the porcine carotid artery (unpublished data).

Thus, inhibition of thrombin activity or thrombin generation prevents all intraluminal thrombus in deeply injured normal porcine arteries. The lipid core of atherosclerotic plaque is

more thrombogenic than arterial media (9), probably because of the presence of tissue factor (1). Evaluation of mechanisms and specific therapies for preventing thrombus on lipid-rich plaques is currently under way.

Growth of Thrombus. Patients who have acute coronary syndromes have a thrombotic substrate of mural thrombus covering the disrupted fatty core of atherosclerotic plaque (1–3) (Fig. 5). This fatty surface is covered with thrombus which is extremely thrombogenic and contains abundant thrombin and factor X_a bound to fibrin (10, 11). Binding of thrombin to fibrin or arterial wall matrix masks receptors on thrombin for antithrombin III and heparin and cofactor II (10, 12, 13). This pretreatment mural thrombus is a thrombogenic substrate for further growth of thrombus which is thrombin dependent and relatively heparin resistant (14). In addition, thrombus generates natural inhibitors of the action of heparin, including platelet factor 4 which is secreted from platelets, and fibrin monomer II, which is generated by thrombin conversion of fibrinogen to fibrin (Fig. 6).

The primary role of thrombin in the growth of thrombus (Fig. 7) is shown by the fact that aspirin alone, usual doses of heparin, heparin combined with aspirin, and even high doses of heparin—which are better than low doses of heparin—do not prevent growth of thrombus on pretreatment mural thrombus. However, the specific

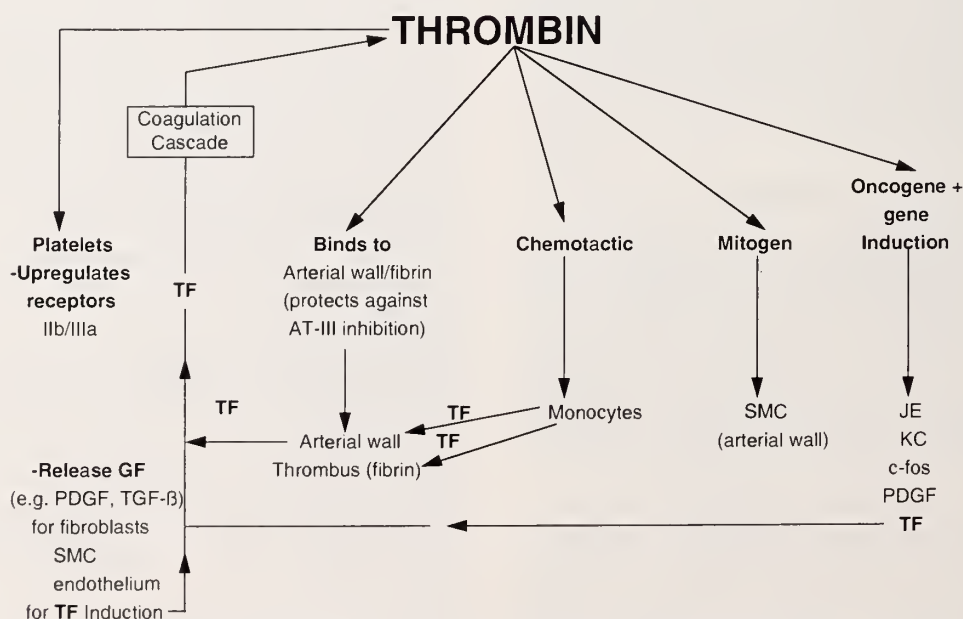


Fig. 2. Thrombin in thrombosis and proliferation: how thrombin begets thrombin in the self-perpetuation of arterial thrombus via the continuing induction of tissue factor, and relationships that also stimulate neointimal proliferation, especially via platelet release of PDGF, platelet derived growth factor, and TGF- β , transforming growth factor- β . TF, tissue factor; AT-III, antithrombin III; SMC, smooth muscle cells; GF, growth factors.

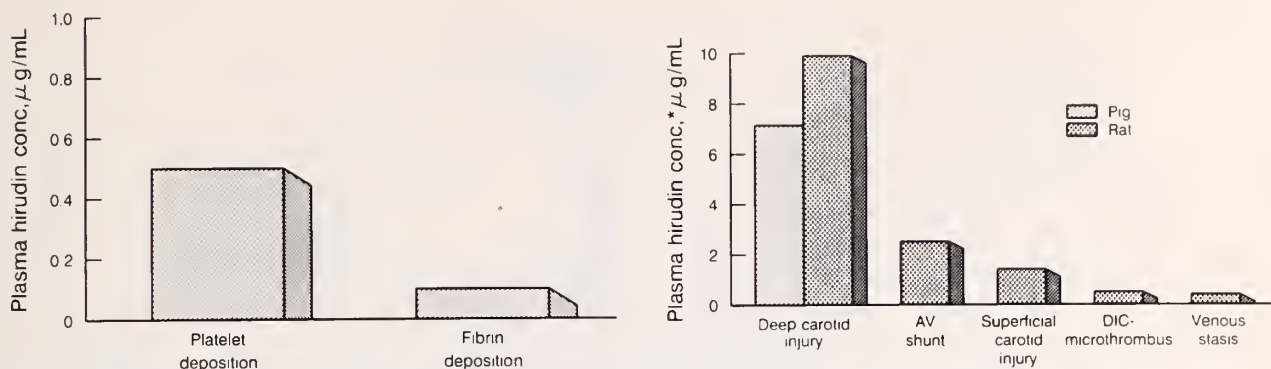


Fig. 3. Left Prevention of microthrombus in the pulmonary circulation in vivo in rats with disseminated intravascular coagulation but no arterial injury. Plasma concentration (conc) of hirudin, the specific thrombin inhibitor, must be five times higher than fibrin microthrombi to totally prevent platelet deposition. Data from Markwardt et al., ref. 56. Right Plasma concentration of hirudin (vertical axis) required to totally prevent intravascular thrombus formation for different thrombotic stimuli of thrombosis (horizontal axis) in rat or pig (data from Heras et al., ref. 7; Markwardt et al., ref. 56; and Ambler et al., ref. 57). Because one molecule of hirudin inhibits only one molecule of thrombin, the blood level of hirudin required to totally prevent thrombosis is an index of the thrombin content or amount of thrombin associated with the different stimuli for thrombosis. AV, arteriovenous; DIC, disseminated intravascular coagulation.

and direct thrombin inhibitor hirudin totally blocks growth of thrombus onto fresh mural thrombus (Fig. 8) and even causes dissolution of significant pretreatment thrombus (15).

The ongoing trials GUSTO IIb and TIMI 9b will extend these studies from animals to human patients in phase III clinical trials.

Maintenance of Platelet Cohesion. Thrombin is necessary for maintenance of platelet cohesion. If thrombus is allowed to grow for 30 minutes after deep arterial injury of the porcine carotid artery and hirudin or placebo treatment is started, after one hour of hirudin therapy, 90% of the platelet thrombus dissipates or "dethromboses"; however, placebo treatment is followed by thrombus increase or progression to total occlusion (16). The specificity of hirudin for thrombin documents that thrombin is necessary for maintaining platelet cohesion. The evidence that TAP, the specific factor Xa inhibitor, also causes dissolution of the 30-minute-old thrombus documents that continued thrombin generation is necessary to maintain platelet-thrombus cohesion.

Consolidation of Thrombus. Thrombin activates factor XIII to XIIIa, which cross-links fibrin and thus consolidates the thrombus (Fig. 7) (17). The length of time over which this occurs in the course of thrombus formation, growth, and maturation is uncertain. In addition, the degree of cross-linking that will hinder and reduce thrombus dissolution or thrombolysis is unclear.

Thrombus Removal and Balance between Thrombosis and Thrombolysis. Thrombosis and lysis are simultaneous, dynamic, and continual reactions. The rate and extent of one process influences the other. Blocking thrombolysis en-

hances thrombosis. This was evidenced clinically in one study in which using aprotinin to block thrombolysis during CABG procedures enhanced vein graft occlusion and acute perioperative infarction (18). In retrospect, it was learned that aprotinin prolongs the activated clotting time (ACT) stimulated with celite but not kaolin; thus, insufficient heparin would have been delivered when the ACT was stimulated with celite (19). Lp(a) is a natural inhibitor of thrombolysis and increases the risk of arterial thrombosis, myocardial infarction, and atherosclerosis (20, 21).

This balance between thrombosis and thrombolysis can be influenced positively by using antithrombotic therapy to enhance thrombolysis. The more potent the antithrombotic therapy, the greater the increase of thrombolysis. This is true both for pharmacologic and for endogenous thrombolysis. For example, the most potent antithrombin, hirudin, maximally accelerates thrombolysis with rt-PA in vivo in pigs, and nearly eliminates residual thrombus within 3–4 hours of thrombolysis, whereas heparin increases activated partial thromboplastin time to over 5 times control, and has only a mild effect, and aspirin has no effect on accelerating thrombolysis or reducing residual thrombus (22). In patients treated with hirudin in the unstable-angina pilot study (23), 10 patients with totally occluded aortocoronary vein bypass grafts were treated only by intravenous infusion of hirudin for 3–5 days; 5 of 10 patients had recanalization of the vein graft (none had thrombolytic therapy). Thus, a potent antithrombotic agent enhanced endogenous lysis and permitted salvage of all vein grafts without

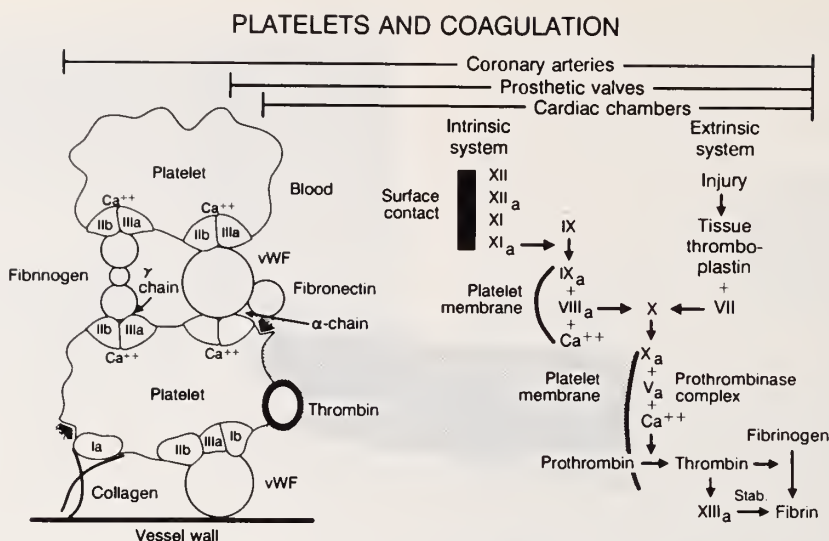


Fig. 4. Biochemical interactions between platelet membrane receptors, vessel wall, and adhesive macromolecules during platelet adhesion and aggregation (left). Also depicted are intrinsic and extrinsic systems of the coagulation cascade and their interaction with the platelet membrane (right), such as via the prothrombinase complex, the activator complex for thrombin. Coronary thrombosis is associated with both platelet and coagulation processes. Ca^{++} , calcium ion; vWF , von Willebrand factor; Ia , glycoprotein Ia ; Ib , glycoprotein Ib ; IIb/IIIa , glycoprotein IIb/IIIa , Stab. Modified with permission from ref. 55.

surgery; all 5 patients had balloon angioplasty of the residual stenosis (24).

Thrombin Activity and Generation. Thrombin activity has traditionally been measured by the blood level of fibrinopeptide A (FPA), which is released in the conversion of fibrinogen to fibrin by thrombin (25). However, this measurement does not indicate the effectiveness of therapy against arterial thrombosis, since platelets may still be activated and form platelet-rich (macroscopic thrombi even if hirudin or heparin block fibrinopeptide A production as shown in vivo in pigs (unpublished data, Heras and Chesebro).

Thrombin generation may be measured by the plasma level of prothrombin fragment 1.2, which is released as prothrombin is converted to thrombin (F1.2 half-life 90 minutes) (Fig. 9). Thrombin generation may also be measured by the blood level of thrombin antithrombin III (TAT), a covalent complex whose formation is accelerated by heparin, half-life 15 minutes, or by measurement of the tightly bound and specific complex of hirudin-thrombin, which has a half-life of 4–6 hours and is measurable in animal and human plasma (26, 27). Measurement of the hirudin-thrombin complex shows that thrombin generation continues in spite of specific and direct inhibition of thrombin by hirudin while prolonging the activated partial thromboplastin time (aPTT) to 60–90 sec (Fig. 10) (27, 28). This con-

tinued thrombin generation is not peculiar to hirudin but also occurs with heparin and other thrombin inhibitors (29). This does not challenge the effectiveness of hirudin but rather may provide important information about the pathogenesis and duration of ongoing thrombosis as well as the requisite duration of antithrombotic therapy. Measurement of prothrombin fragment 1.2 and fibrinopeptide A have shown acute elevation of thrombin generation and activity at the onset of acute coronary syndromes and the persistence of increased thrombin generation for as long as 6 months after the acute episode (25). Reasons for this persistent thrombin generation are uncertain and are currently under investigation.

There may be long-term benefit from reduction of residual thrombus during treatment of acute coronary syndromes. First, reduced residual thrombus would reduce luminal obstruction, perhaps back to the minor (<50%) stenosis that antedates most plaque disruptions (1). Second, reduction of residual thrombus may reduce the proliferative response to arterial injury. Specific thrombin inhibition with hirudin for two weeks has also reduced iodine ^{125} fibrinogen deposition and the proliferative response measured by (a) neointimal area (particularly the area encroaching on the lumen but not the area filling in arterial wall dissections and fissures) and (b) immunohistochemical staining for nuclear bromode-

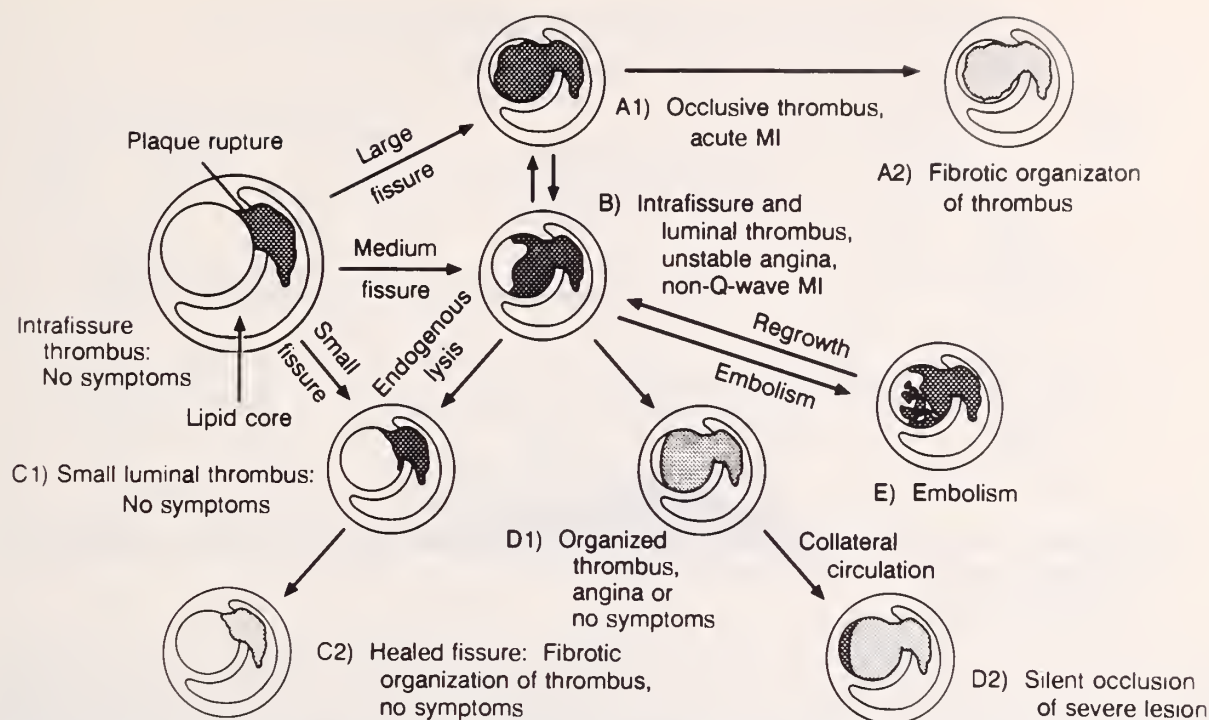


Fig. 5. Major pathogenic modes of progression of coronary disease. Plaque rupture leads to formation of a fissure with flowing blood contacting intra-arterial structures and forming intrafissure thrombus. This may not progress or lead to symptoms (except for possible sudden onset of coronary spasm or vasoconstriction associated with arterial injury). Fissure may be small, medium, or large and may progress immediately to various degrees of luminal obstruction (A1, B, or C1). Sudden progression with large fissure may be due to occlusive thrombus and acute myocardial infarction (MI), A1. Fibrotic organization of thrombus may occur (A2), or thrombolysis (exogenous or endogenous) may occur and reopen lumen to partial obstruction (B). Medium-sized fissure may lead to immediate partial obstruction associated with unstable angina or non-Q-wave MI (B); this may progress to total occlusion (A1), partial embolization of thrombus (E), fibrotic organization of thrombus (D1), endogenous lysis to a small thrombus (C1), or no intraluminal thrombus. Residual thrombus may undergo fibrotic or fibromuscular organization (A2, C2, and D1). Severe residual stenosis (D1) may be associated with good collateral circulation and no symptoms. Because of low antegrade flow and type II injury (endothelial denudation only) but no deep injury, this may silently occlude with fresh thrombus (D2). Small fissure may lead to small thrombus without symptoms (C1) and undergo fibrotic organization with progression of disease in the absence of symptoms (C2). *Reproduced with permission from Chesebro et al., ref. 3.*

oxyuridine (administered during a period of 48 hours before the two-week euthanasia) (30).

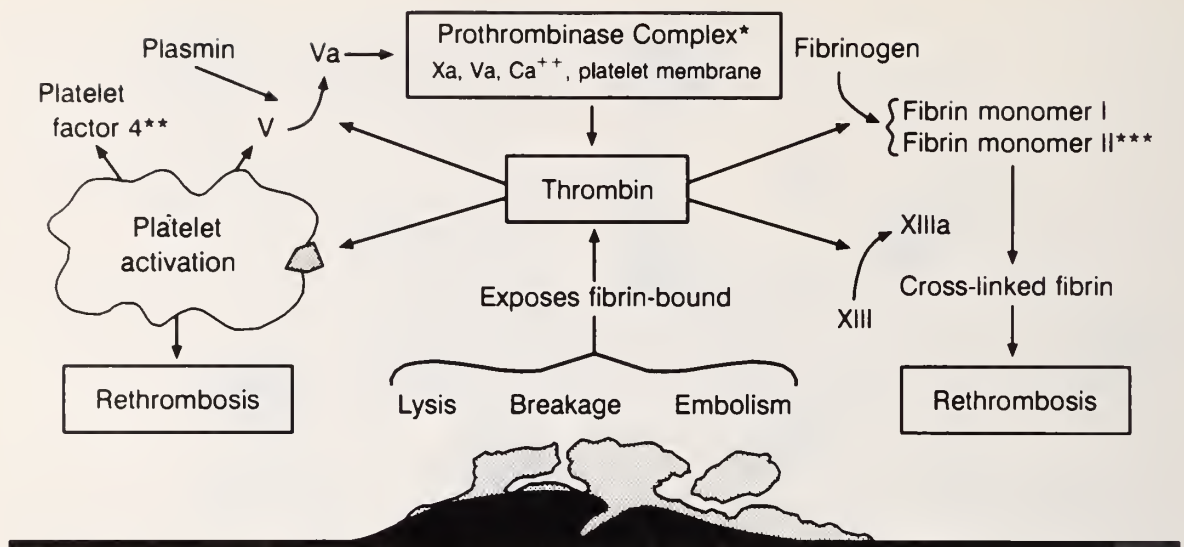
Vasoconstriction after Arterial Injury. The role of coronary vasospasm in the pathogenesis of unstable angina or after arterial injury (by spontaneous plaque disruption or after PTCA) is suggested by the findings of hemodynamic, ECG, and angiographic studies. Vasoconstriction associated with acute arterial injury is platelet dependent, endothelium dependent, and endothelin dependent (lipid infiltration into the arterial wall stimulates endothelin production in the wall) and may be reduced by intravenous nitroglycerin, reduction of platelet-rich thrombus, or both (31–34).

The severity of vasoconstriction and the amount of platelet deposition are directly related (32). Aspirin reduces platelet deposition and vasoconstriction but does not eliminate either one. Thrombin appears to enhance vasoconstriction because it stimulates release of endothelin-1, a potent vasoconstrictor (33). Vasoconstriction as-

sociated with human angioplasty is delayed for approximately 15 minutes after the procedure and can be reduced by the infusion of intravenous nitroglycerin but is not prevented by routine oral therapy with calcium channel blockers (34).

Antithrombin Therapy

Not all thrombin inhibitors are equally effective (35). Specific dose-response evaluation for optimal doses to inhibit fibrin and platelet deposition must be performed for each inhibitor (6, 7). The dramatic response—no macroscopic thrombus after deep arterial injury—during specific thrombin inhibition with hirudin led us to search for a source of thrombin generation in the arterial wall. After injury, thrombin in arterial wall tunica media has been demonstrated by immunohistochemical staining with an antibody specific for thrombin; in addition, after incubating the artery with hirudin, there is positive staining with



*Protects Xa from heparin-antithrombin III

**Neutralizes heparin

***Inhibits heparin-antithrombin III interaction with thrombin

Fig. 6. Disturbance of thrombus by lysis (endogenous or exogenous), mechanical breakage (including coronary angioplasty), or spontaneous embolism exposes thrombin bound to fibrin. Thrombin activates platelets, activates factor V to Va (which leads to generation of more thrombin via prothrombinase complex), converts fibrinogen to fibrin I and fibrin II, and activates factor XIII to XIIIa (which crosslinks fibrin). These processes combine to produce rethrombosis. Heparin may only partially prevent rethrombosis because factor Xa within the prothrombinase complex is protected from heparin-antithrombin III, platelet factor 4 neutralizes heparin, and fibrin monomer II inhibits heparin-antithrombin III interaction with thrombin. *Reproduced with permission from Webster et al., ref. 58.*

antithirudin antibody. Subsequently, prothrombin has been extracted from smooth muscle cells which may provide substrate for thrombin generation after arterial injury (36).

Experimental studies in rabbits using selective depression of individual vitamin K-dependent clotting factors suggest that prothrombin and factor X are pivotal for inhibition of thrombin generation by the coagulation cascade (37). Thus, it is not surprising that warfarin may totally prevent thrombus in injured arteries (8). In addition, thrombin upregulates glycoprotein (GP) IIb/IIIa receptors on platelets (Fig. 4), and prostacyclin closes IIb/IIIa receptors (38). Thus, marked inhibition of thrombin may obviate the need for antiplatelet therapy or may reduce the dose requirement for platelet inhibition (such as a GP IIb/IIIa receptor inhibitor).

Dosage. Three principles are important for choosing the dosage of a given antithrombin therapy. These principles probably apply to most antithrombotic drugs.

First, the dose-antithrombotic response of a thrombin inhibitor is not linear but rather shows a threshold response (Fig. 11). In the dose-response of hirudin for the prevention of mural, subocclusive thrombus, considerable thrombus was present at an aPTT of 1.7 times control, but

no thrombus was present when the aPTT reached 2.0 times control (7). This is probably because only minute amounts of thrombin are necessary for platelet deposition (5). This threshold response needs to be defined for each individual thrombin inhibitor.

Other direct thrombin inhibitors that we have evaluated and that have a lower binding affinity than hirudin have not had sufficient potency to totally prevent mural thrombus (35). Unless mural thrombus is totally prevented, we are not able to test for a threshold dose-response. It does appear that thrombin inhibitors with a lower binding affinity must be given in increased drug doses with higher aPTTs to produce a sufficient antithrombotic effect.

Second, short-term (24–48 hours) hirudin therapy does not prevent the return of thrombus on deeply injured arterial surfaces in pigs when the arteries are examined histologically 24 hours later (Webster MWI and Chesebro JH, unpublished data). Thus, one cannot administer short-term hirudin for a few days and expect a lasting response weeks or months later, and stopping antithrombotic therapy arbitrarily does not mean that thrombogenicity of the injured artery has disappeared and will not cause a thrombotic response. This may explain the results of the HEL-

ARTERIAL DAMAGE AND THROMBOSIS

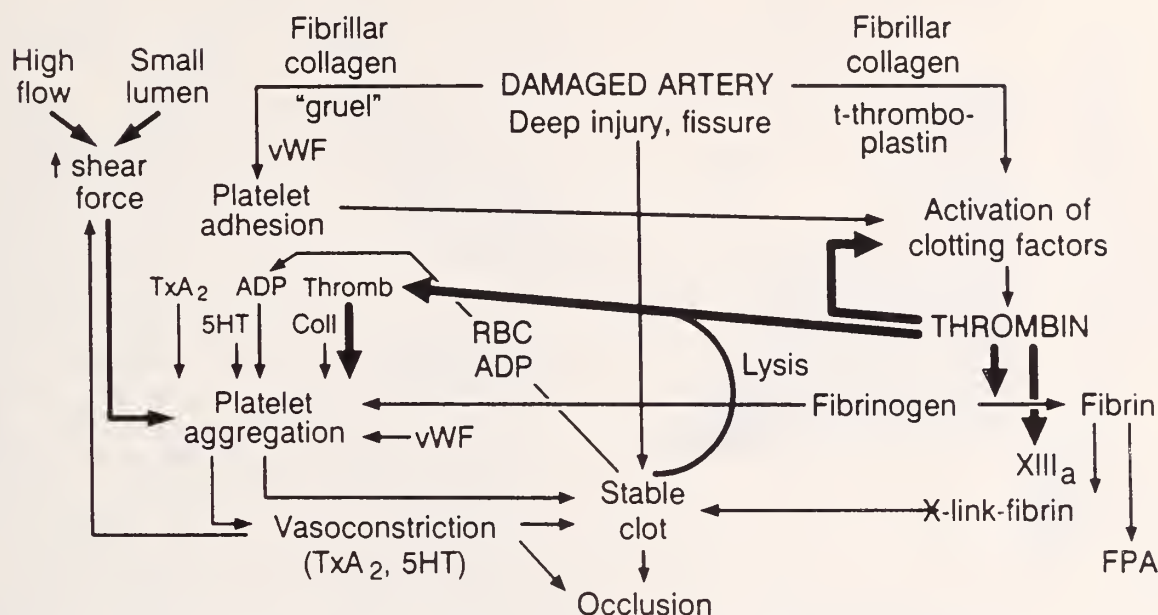


Fig. 7. Diagram showing proposed mechanism of arterial thrombosis. Fibrillar collagen from exposed media, "fatty gruel" from the atherosclerotic plaque, and tissue factor, which activates factor VII to VIIa; factor VIIa activates factor X to Xa, which helps generate thrombin; thrombin activates platelets, which adhere to the arterial wall via the von Willebrand factor; thrombin-activated platelets release thromboxane A_2 , serotonin, and ADP, which (together with the ADP from the red blood cells trapped in the thrombus) cause additional platelet aggregation. Activation of the coagulation pathways leads to production of the prothrombinase complex on the platelet and smooth muscle cell phospholipid membrane, which binds Ca^{++} and factors Va and Xa; this accelerates the production of thrombin by 280,000 times. Thrombin is the major activator of platelets and converts fibrinogen to fibrin, releasing fibrinopeptide A (FPA) and fibrin II monomer (which inhibits heparin-antithrombin III inactivation of thrombin). Fibrinogen/fibrin binds to platelet glycoprotein IIb/IIIa receptors and forms bridges between platelets. The activation of factor XIII by thrombin causes a cross-linking (X-link) of the fibrin strands and a stabilization of the new thrombus. TxA_2 , thromboxane A_2 ; vWF, von Willebrand factor; ADP, adenosine diphosphate; RBC, red blood cells; 5HT, 5-hydroxytryptamine (serotonin). Modified with permission from Heras M et al., *Thrombolysis in Cardiovascular Disease*, chap. 11, New York: Marcel Dekker, 1989, pp 203–229.

VETICA study, in which hirudin was effective for the 96 hours during which therapy was administered but had no lasting effect at 7 months (39).

Third, the ideal dose of any antithrombotic therapy, such as hirudin, would produce an immediate increase in the blood level to the plateau level that prevents formation and growth of thrombus without exceeding that level with an initial bolus. The maintenance dosing should keep this optimal plateau level. In order to achieve this, mechanisms of elimination and metabolism should be known not only in normal subjects but also in patients of different ages and with the disease process under study. For example, hirudin is excreted entirely by the kidney, has a half-life of 50 minutes in normal subjects under age 40, but has a considerably longer half-life of 2–3 hours in stable patients with coronary artery disease and a mean age of 60 years (40). It is likely that the half-life is even longer in patients with acute myocardial infarction, whose pain and stress are likely to have increased blood

catecholamine levels, which probably reduces renal excretion. These factors relating to drug excretion may have, in part, contributed to the higher aPTTs in a certain subset of patients who were at higher risk of intracranial hemorrhage (when the aPTT was a mean of 115 sec) compared to those who suffered no bleeding (mean aPTT 85 sec) (41–43). These aPTTs were measured at 12 hours. It is likely that the initial aPTTs after the intravenous bolus were considerably higher.

Improvement in the choice of endpoints for doses of new antithrombotic therapies in humans is needed. The endpoints of death, myocardial infarction, or acute arterial occlusion are not sufficiently precise and place patients at danger. Endpoints should involve the growth of mural thrombus starting with ex vivo platelet deposition, which correlates well with in vivo dosing (6, 7, 14), and proceed to growth of thrombus using platelets labeled with indium 111 or technetium 99m over areas of arterial injury such as following angioplasty or arterial endarterectomy or by-

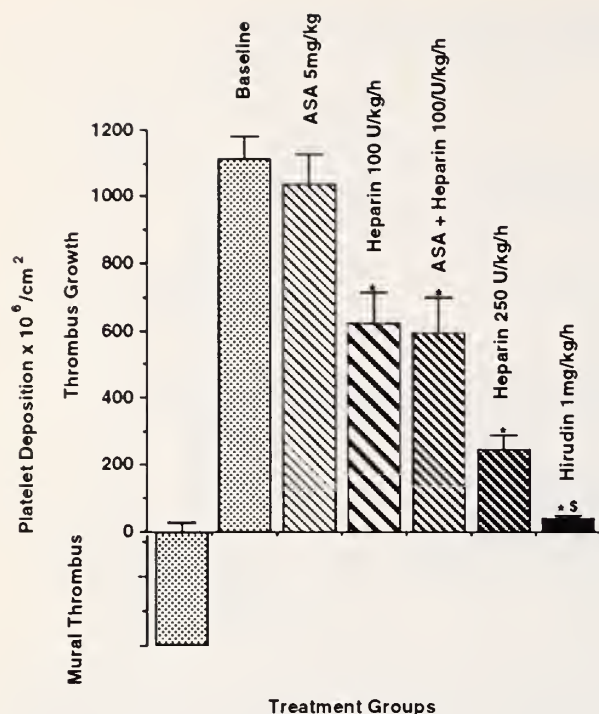


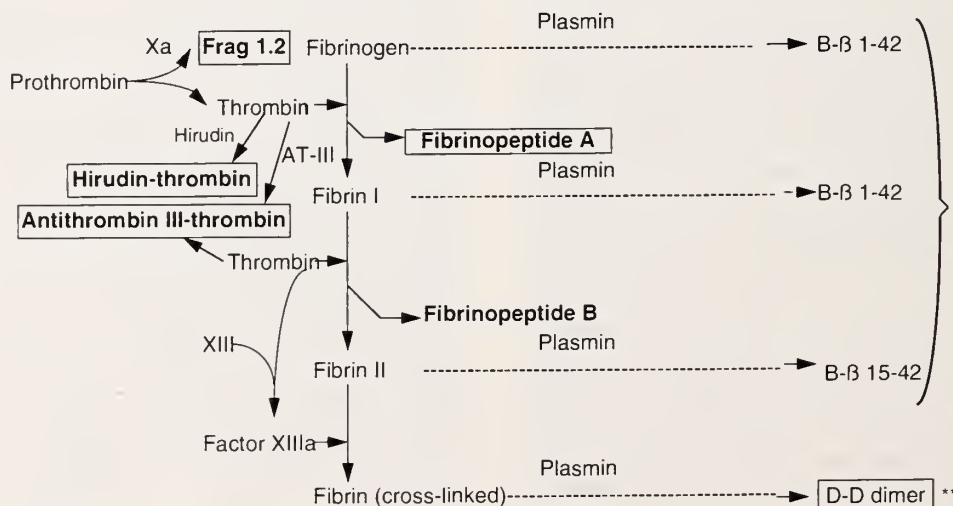
Fig. 8. Differential effects of antithrombotic regimens on mean platelet deposition during growth of thrombus triggered by a fresh mural thrombus at high shear rate. Vertical lines, SEM. Aspirin (ASA) had no significant effects on growth of thrombus. Heparin showed a dose-dependent effect on growth of thrombus. Platelet and fibrinogen depositions in animals treated with hirudin were significantly lower than in the highest-dose heparin group (* $P < .05$ vs baseline, $^{\$}P < .001$ vs heparin 250 IU/kg). Reproduced with permission from Meyer et al., ref. 14.

pass graft procedures. Measurement of growth of thrombus rather than total occlusion would give a more precise dose-response that would require fewer study patients and improve the safety of the studies.

Blocking Growth of Thrombus. In patients with unstable angina, heparin alone is superior to aspirin alone in preventing acute myocardial infarction (0.8% vs. 3.7%) during hospitalization (44). However, aspirin appears to be necessary to reduce the risk of reactivation events when heparin is stopped or if anticoagulation falls below an activated partial thromboplastin time (aPTT) of $2 \times$ control or 60 seconds (45). Retrospective studies suggest that heparin administered for at least 3 days prior to coronary angiography will reduce the risk of complications for patients who undergo coronary angioplasty (46–49). Heparin plus aspirin converted to warfarin plus aspirin appears promising for acute coronary syndromes (50).

After thrombolysis for myocardial infarction, the lowest incidence of angiographic reocclusion is in patients who receive heparin (aPTT 60–85 sec) plus aspirin (80–160 mg/day). This combination was documented in the GUSTO angiographic study, in which reocclusion rates were the lowest reported in the literature and ranged from 4.9%–6.4% from arteries patent at 90 min to repeat angiography after 5–7 days in each of the four treatment groups (51). Although short-term heparin

BIOCHEMICAL MARKERS OF FIBRIN AND THROMBIN FORMATION AND FIBRINOLYSIS



* Plus other soluble, uncross-linked fibrinogen degradation products

** Plus other soluble, cross-linked fibrin degradation products

Fig. 9. Formation of biochemical markers during conversion of prothrombin to thrombin and fibrinogen to fibrin and during fibrinolysis. These markers can be measured in plasma and indicate extent of ongoing chemical conversions.

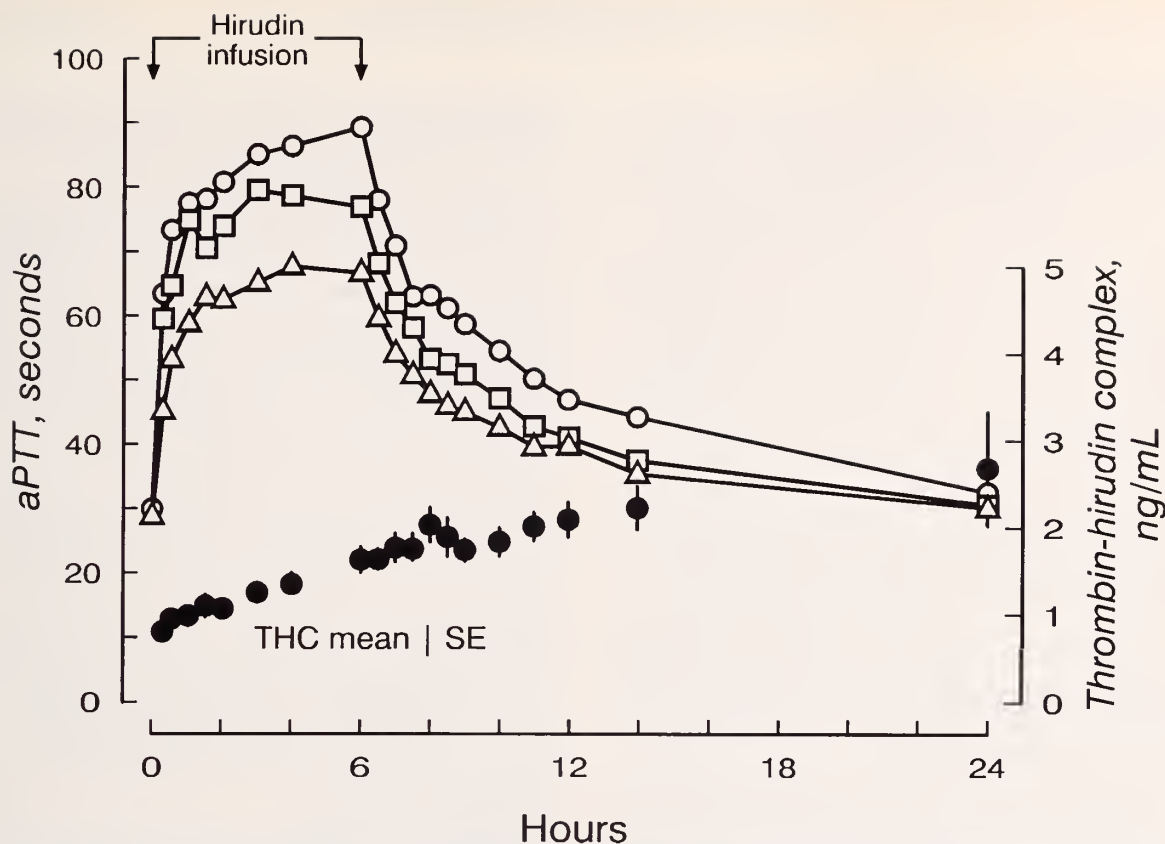


Fig. 10. Plot of effect of recombinant hirudin on intravenous thrombin-hirudin complex and activated partial thromboplastin time (aPTT). Mean aPTTs of all 18 subjects receiving a 6-hour infusion of hirudin at 0.3 (○), 0.2 (□), or 0.1 (△) mg/kg⁻¹/h⁻¹ and mean thrombin-hirudin complex (●) for all subjects. Bars indicate SEM. Reproduced with permission from Zoldhelyi et al., ref. 27.

PREVENTION OF THROMBOSIS DURING ANGIOPLASTY Mural Thrombus in Deep Arterial Injury

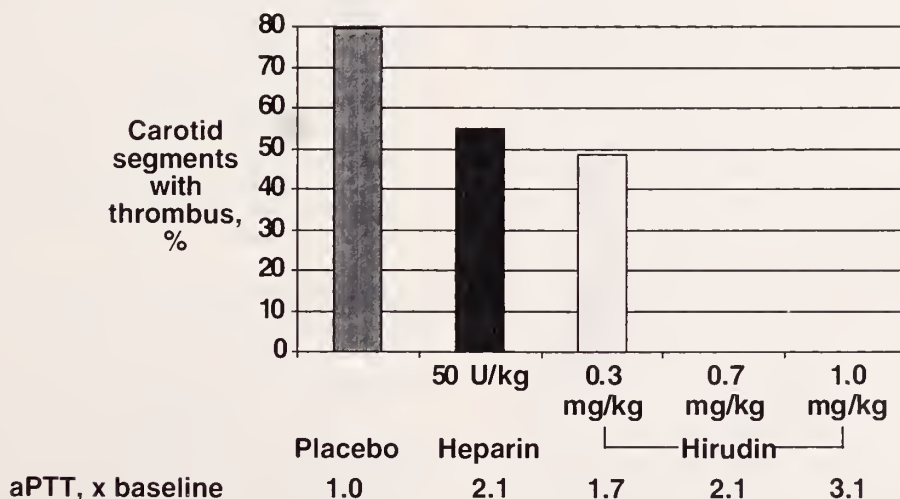


Fig. 11. Threshold dose-antithrombotic response to three different doses of hirudin, placebo and a single dose of heparin. Ordinate, incidence of mural thrombus on deeply injured porcine carotid arteries after angioplasty; abscissa, drug doses and aPTTs. Note high incidence of thrombus for hirudin aPTT 1.7× control and no thrombus for hirudin aPTT 2.0× control. Data from Heras et al. 1990, ref. 7.

TABLE
Pooled Analysis of Relative Risk of Combination Therapy
versus Aspirin Alone

Trial	Myocardial infarction % or death at 5 days	
	Aspirin (n)	Aspirin + heparin (n)
ATACS (50)	8.3% (109)	3.8% (105)
RISC (53)	3.7% (189)	1.4% (210)
Theroux et al. (54)	3.3% (12)	1.6% (122)
RR _{mh} (CI) .44 (.21-.93)		

Reproduced with permission from Cohen et al. (Ref. 50).

therapy for 24 hours followed by aspirin alone is said in one study to be equal to continued heparin therapy for one week (without aspirin) (52), neither of the study groups had a satisfactorily low rate of occlusion (20% occlusion in both groups). Thus heparin plus aspirin should be continued for the duration of hospitalization to assure a sufficiently low reocclusion rate.

Pooling of data from three randomized trials documents the superiority in preventing myocardial infarction and death during the first 5 days of hospitalization of heparin plus aspirin over aspirin alone in patients with unstable angina or non-Q-wave myocardial infarction (50, 53, 54) (Table). Heparin plus aspirin and the conversion of heparin to warfarin is superior to aspirin alone in reducing coronary events in the early days and months after unstable angina or non-Q-wave myocardial infarction (50).

Doses of heparin higher than those administered in GUSTO I (5000 U bolus + 1000 U/h infusion to aPTT 60–85 sec) for patients receiving thrombolytic therapy (but not for those who did not receive lytic therapy) resulted in an increased incidence of intracerebral bleeding ranging from 1.5% to 1.9% of patients, regardless of thrombolytic agent (41, 42). In these trials, the dose of heparin was increased approximately 15%–20% above that of GUSTO I. The European trial used heparin in a dose range approximately 10% lower than that of GUSTO IIa (intravenous heparin 70 IU/kg body weight bolus and 15 IU/kg per hr infusion), and observed no intracranial hemorrhages in a small number (154) of patients (43).

Future goals include more potent antithrombotic therapy to encourage increased endogenous lysis of residual mural thrombus and a reduction in the residual stenosis which is often caused by acute thrombus. Future therapies that may block thrombosis sufficiently to allow endogenous lysis include a combination of warfarin plus aspirin, or a specific thrombin inhibitor such as hirudin, which inhibits both fibrin and platelet deposition

after deep injury (6, 7, 14, 24, 50). It is uncertain whether additional therapy will be needed and what duration of therapy is necessary.

Current Recommendations. Maximal antithrombotic therapy for acute coronary syndromes includes an intravenous bolus of heparin of 5000 U, followed by an intravenous infusion at 1000 U/hr to maintain the activated partial thromboplastin time at 2–3 times control (60–85 sec) for at least 5–7 days. To convert intravenous to subcutaneous administration, use 14,000–17,000 U every 12 hours (target aPTT 60–85 sec at 8–12 hours after subcutaneous dose) and continue intravenous dose for 2 hours after first subcutaneous dose. The loading dose of aspirin on admission to the hospital is 160–325 mg, followed by 80–160 mg/day. For most patients, conversion of heparin to warfarin therapy should be considered for at least 3 months at an international normalized ratio of 2.0–3.0 for the prevention of recurrent ischemia, reinfarction, death, thromboembolism, reactivation of thrombosis, and reduced necessity for revascularization.

Because warfarin when combined with aspirin may be equally effective in doses lower than now recommended, the Coumadin Aspirin Reinfarction Study was designed using fixed dose warfarin at 1 mg a day plus ASA 80 mg, versus 3 mg warfarin a day plus ASA 80 mg, versus ASA 160 mg alone. The study endpoint during 3–4 years of follow-up is the combined endpoint of reinfarction, death, and stroke. Entry of patients will be complete by the end of 1995.

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Prevention of Remodeling of the Heart after Myocardial Infarction

RICHARD GORLIN, M.D.

Abstract

Secondary prevention is critical following myocardial infarction. Infarct expansion leads to cardiomegaly, which may adversely affect prognosis. Infarct expansion seems to be associated with hypertension, anterior location, persistent (probably sudden) occlusion of the infarct artery, and poor collateralization. Prevention of cardiomegaly by angiotensin-converting-enzyme inhibitors, and possibly nitrates, seems to improve survival. Angiotensin-converting-enzyme inhibitors seem to delay the onset and the frequency of congestive failure and recurrent myocardial infarction.

IN TREATING PATIENTS who have suffered a myocardial infarction (MI), efforts can be made in the months after the event to contain damage to the heart and to improve survival. In the past, attention has concentrated on the acute phase of the infarction, with less emphasis on the later course of the disease. We now better understand how the heart changes following MI, what some of the implications of these changes may be, and what we can do about them.

Prevention of secondary consequences of MI currently aims at modifying the processes leading to congestive heart failure. Therapy extends beyond treatment of the primary myocardial injury to include attenuation of the adaptive remodeling, hypertrophy, and enlargement that inevitably follow. Pfeffer (1) documented the complex progression—through infarct expansion, wall thinning, and left ventricular dilation to left ventricular failure—that occurs over approximately three to five months following MI (Fig. 1).

Ventriculographic studies taken in the first day or two following acute myocardial infarction, and then two weeks later, show that by the end of

two weeks the perimeter of the infarct zone may or may not be about the same length as at the first reading (2), but that the heart overall has lengthened and widened modestly. This morphologic change is only one kind of alteration. The region of the infarct may also expand, with concomitant thinning of the damaged tissue. Thus, both the infarcted tissue and the uninvolved myocardium contribute to secondary compensatory changes following MI.

Postinfarct cardiac enlargement may be progressive over at least the first year (3). At first this may appear to represent the Starling mechanism but it does so only up to a point. Ertl et al. (4) plotted left ventricular end-diastolic volume against stroke volume to produce a modified Starling curve. These workers found that the volume of the heart increased after MI initially, with a concomitant increase in stroke volume. Over 5–8 months, however, heart size continued to increase to a volume of over 90 mL, with absolutely no change in stroke volume. This is a pathologic condition in which the heart has dilated without augmentation of stroke work, so the Starling effect is to no avail.

Significance

Does this have any implications that influence our approach to the patient? Two valuable

Adapted and updated from the author's Grand Rounds presentation at the Mount Sinai Medical Center on January 19, 1993. Address correspondence to: Richard Gorlin, M.D., Senior Vice President, The Mount Sinai Medical Center, Box 1018, One Gustave L. Levy Place, New York 10029.

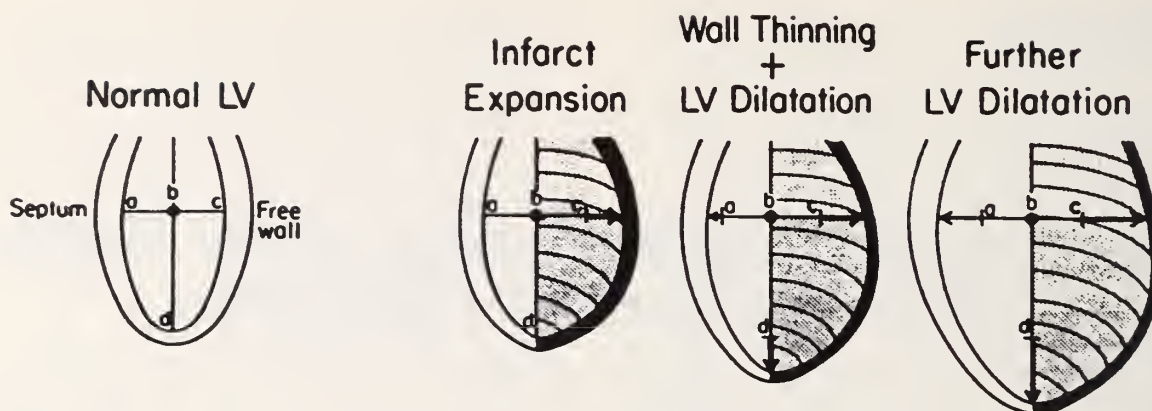


Fig. 1. Left ventricular volume changes over 106 days following myocardial infarction: from expansion of the infarct through myocardial wall thinning, dilatation, and finally further dilatation. Reprinted with permission from ref. 1.

studies address this question. The first, from the Veterans Affairs Medical Center in Seattle (5), examined end-diastolic and end-systolic volume indices and the number of deaths occurring in patients in the years following a myocardial infarction. With mild cardiac enlargement there was a moderate increase in the number of deaths per thousand patient years. Beyond that, with as little as a 35% increase in volume, mortality in-

creased by a factor of 3–4. The end-systolic volume showed the same association between increased heart size and negative outcome.

A similar study by White et al. (6) (Fig. 2) found that when the ejection fraction is greater than 0.50, increased end-systolic volume does not seem to affect survival, but when the ejection fraction decreases by as little as 0.10, the size of the heart becomes important. When the end-systolic volume in this study was greater than 95 mL, 50% of the patients had died by the end of seven years. If the ejection fraction was less than 0.40, and the heart even larger, by the end of only six years 60% had died. How well the heart contracts and how big it is, taken together, can accurately predict mortality. Whether ability to contract and tendency to enlarge can be changed is the question we need to address.

Factors leading to Cardiac Enlargement

Factors leading to cardiac enlargement include infarct expansion relatively early during the acute event, leading to local ventricular dilatation. During the first few weeks, two processes are at war with one another: continued expansion and healing of the infarct area. This healing process, because it changes the shape at the infarct zone, leads to increased stress in the wall of the heart and to generalized ventricular dilatation over the ensuing months (7).

Routine echocardiography is the best technique for monitoring this process. Testing can be done in any cardiac care unit during the course of the infarct or afterward and should become standard practice through and well beyond the acute phase of myocardial infarction. Using the 2-D method, the heart can be examined in "slices" and one can document thinning and bulging of the

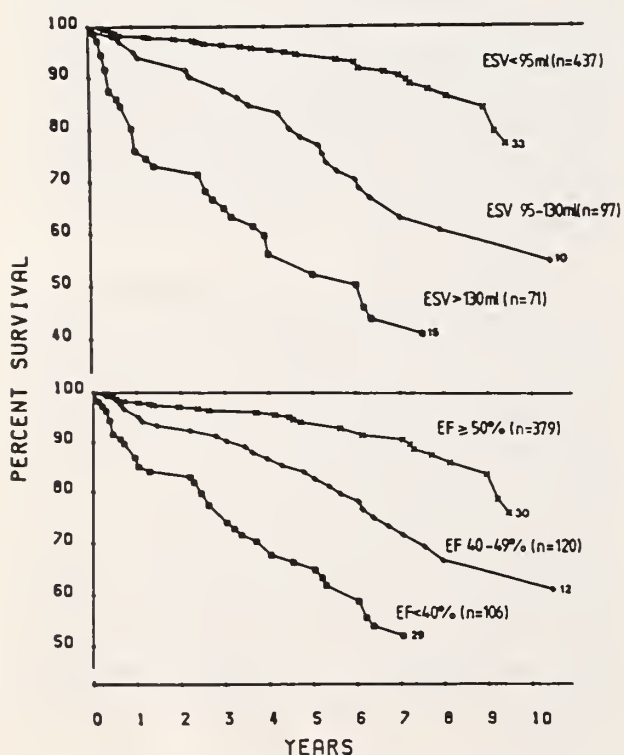


Fig. 2. Actuarial survival curves for patients in three groups by end-systolic volume (ESV) (top) and by ejection fraction (E-F) (bottom) following recovery from acute MI. Difference between groups is wider with ESV than with EF. Numbers after last data points indicate number of patients at risk during last year of follow-up. Reprinted with permission from ref. 6.

infarct area as well as developments in the rest of the cardiac chamber.

Sequential echocardiograms over the course of time (8) (Fig. 3) show that after the first few days, thinning and rounding out of the infarct zone occur in about half the patients. Finally, at one month, this structure is often thin and box-like, with dilation of the noninfarct chamber as well. Even while the patient is still in the cardiac care unit, some dilatation and distortion of shape occur, but serious deformations appear only later (9), and not in every patient.

One of the most important factors influencing the degree of remodeling seems to be the depth of transmural insult inflicted by the MI. This is difficult to quantify in the clinical setting. Categorizing the infarction by ECG as "Q-wave" or "non-Q-wave" is not adequate. As the depth of myocardial wall injury increases, there is a progressive decrease in shortening during contraction (10). This correlates with the gradual thinning of the wall.

Certain clinical factors help identify patients at greatest risk (11). Foremost is hypertension. If the patient has had preexisting hypertension, expansion of the infarct is more likely than in normotensive patients. It is critical to evaluate blood pressure at the time of acute MI against the history of known blood pressure levels beforehand. The second important predictor of expansion and its attendant high mortality is anterior myocardial infarction. Thus, hypertension, anterior infarct, and the depth of transmural insult all predispose to thinning and expansion, and probably to high mortality.

Completeness and Suddenness of Flow Deprivation

The completeness and the suddenness of flow deprivation seem to affect post-MI remodeling. Kim and Braunwald (12) examined whether the infarct-related artery was patent after the MI and then measured left ventricular volumes three weeks and 12 months afterward. There was little change in ventricular volume at the end of the year when the infarct-related artery was patent early on. When the vessel was occluded, there were major changes. Ventricular volume increased early and worsened considerably over the year. Something about the borderline supply of blood to the heart becomes important.

Jeremy et al. (13) observed left ventricular volume one month after acute MI and correlated any change in volume with the blood supply to that segment of the ventricle. In patients who had

a subtotal occlusion, ventricular volume showed little or no change one month after the infarct—quite possibly evidence of postocclusive recanalization. Patients who had a persistent total occlusion but good collateral blood supply similarly underwent no change. On the other hand, those who had no collaterals and a total occlusion had a substantial increase in left ventricular volume. Persistent deprivation of blood supply seems to be important in producing cardiac enlargement. In this study, of the 16 patients who had cardiac enlargement, 8 developed clinical congestive failure. Of 24 patients who had no increase in left ventricular volume, only one developed congestive failure. Clearly, there is an association between volume change and clinical consequences.

Finally, Cigarroa et al. (14), following patients over a decade, found a major difference in the outcome between patients whose infarct-related vessel was patent after an MI and those in whom it was closed (Fig. 4).

The Western Washington Study of intravenous streptokinase infusion for acute MI (15, 16) reported similarly that at the end of a year, patients who exhibited complete or even partial reperfusion had a much better prognosis than those who had no reperfusion at all. So patency of the infarct artery is a serious concern.

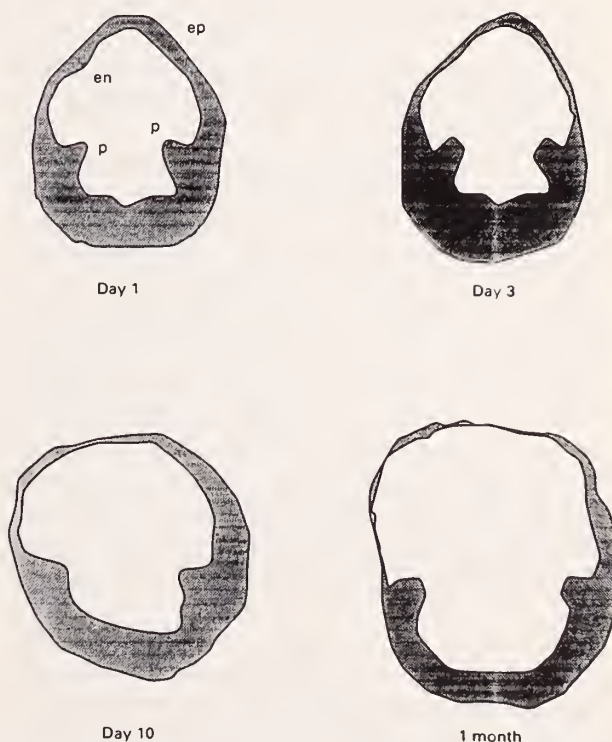


Fig. 3. Serial cross-sectional short axis echocardiograms in anterior MI showing infarct expansion and global ventricular dilatation; en, endocardium; ep, epicardium; p, papillary muscles. Reprinted with permission from ref. 8.

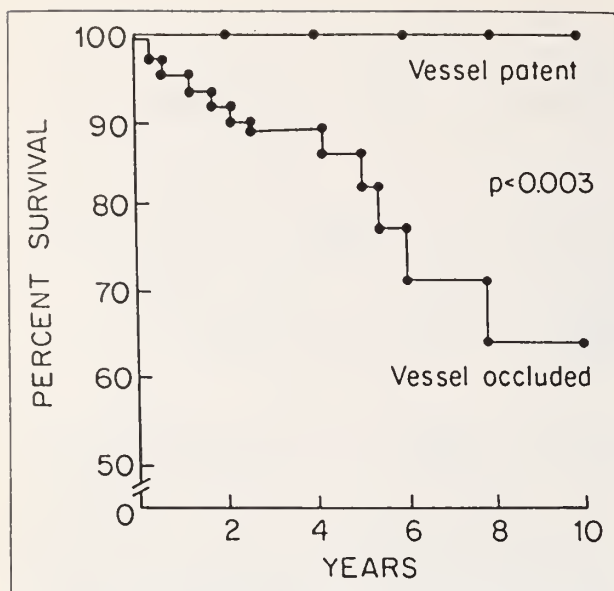


Fig. 4. Survival analysis of patients with patent and occluded infarct-related arteries. Reprinted with permission from ref. 14.

What happens after an MI if the coronary artery is still closed and there are no collaterals? Should revascularization be deliberately attempted? The answer is as yet unclear.

Can Cardiac Enlargement Be Attenuated?

Therapy during the acute phase may attenuate expansion of the infarct and subsequent left ventricular dilation.

Nitrates. Nitrates may play a favorable role in acute myocardial infarction in three ways: they affect afterload and coronary blood supply, and—perhaps most important—have an impact on the venous bed. Nitrates effect venodilation as no other agent does by increasing capacitance, reducing preload, and unloading both left and right ventricles. The results are improved hemodynamics and improved left ventricular geometry. With this comes a reduction in left ventricular filling pressure and volume. There is improvement, or at least maintenance of the status quo, in stroke volume. Deforming wall forces are reduced. The outcome is attenuation of akinesis in the infarct segment.

During the course of acute MI, Jugdutt et al. (17, 18) gave low-dose intravenous nitroglycerin alone for 48 hours, whether or not there was a clinical reason, such as heart failure or pain. Normotensive patients whose blood pressure was lowered only 10–15 mm Hg had smaller creatine ki-

nase infarct size, less left ventricular dysfunction, better global ejection fraction, less infarct expansion and thinning, better clinical status and hemodynamics, fewer complications, and lower mortality. During the first 48 hours, and then at 10 days following the acute event, controls with anterior wall infarction registered a shift upward in the expansion index, and those with an inferior wall infarct had a slight shift upward as well. The expansion index remained unchanged in patients given nitroglycerin. Jugdutt et al. also found that nitroglycerin had a favorable effect on the morphology of the ventricle when they calculated the thinning ratio versus the expansion index in the region of the infarct.

This group confirmed the work of others (19) showing that introducing nitroglycerin early in the course of the infarct favorably modifies the levels of cardiac enzymes. When nitroglycerin was introduced within four hours of the onset of pain, there was a reduction in CK compared with controls. There were also fewer complications, such as infarct expansion, infarct extension, heart block, incidence of thrombus, shock, and in-hospital mortality. Although this was not a mortality study, survival beyond the first year was significantly higher in the nitroglycerin-treated group. As noted earlier, mortality for patients with anterior myocardial infarction is often higher than for those with inferior MI.

A meta-analysis by Yusuf et al. shows the same statistical trend favoring the use of nitrates in the acute phase of myocardial infarction (20).

Beta Adrenergic Blockade. Beta blockers deserve mention for their role in preventing cardiac rupture during the acute phase. The ISIS-1 trial (21) examined autopsy results of acute MI patients who had received atenolol or placebo. Most of the survival benefit occurred during the first two days and was attributable to attenuation of cardiac free-wall rupture—an extreme form of remodeling. There was no difference between the groups for other causes of death (22). Beta blockers seem to provide mechanical protection during the first day of a myocardial infarction, which may enhance long-term advantage as well.

Thrombolytic Therapy. Thrombolytic therapy is now used routinely in acute MI. In one study, 30 days after thrombolytic therapy for an inferior MI, there was no difference in left ventricular volume between patients who had received thrombolysis and those who had not (23). In anterior wall infarction, however, both left ventricular end-diastolic and end-systolic volume were lower in those who received thrombolytic

therapy than in controls. Hence, thrombolytic therapy does attenuate the increase in ventricular volume, at least for anterior wall infarcts.

Another issue concerning thrombolytic therapy and heart size deserves consideration: the timing of thrombolytic intervention in relation to the onset of pain. Is there some late benefit? Two studies are worth noting. The first is an experiment by Hochman (24), which examined the effects of ligation and reperfusion of the coronary artery in rats. The first group had a 30-minute ligation to occlusion and were then reperfused. The second ligation was held for two hours, then reperfused. In the third group, the ligation was left on permanently. In the group undergoing two hours of ligation before reperfusion, the infarct size was much larger than in the group whose ligation was removed at 30 minutes; in fact, the outcome was no different from that in the group whose ligation was permanent. Infarct expansion in the rats with a permanent ligation was nearly double that of the group which was perfused at 30 minutes. With late reperfusion, however, there was only moderate expansion of even a large infarct. This suggested that infarct size and remodeling may be influenced differently by time to reperfusion.

Bonaduce (25) looked at this issue in a clinical study. He compared those patients who received tissue plasminogen activator (tPA) within four hours of MI with those receiving tPA within the four-to-eight-hour interval and with those receiving no thrombolysis. Examining only left ventricular end-diastolic volume, there was a step-wise increase from those receiving early tPA, to mid-late tPA, to none at all. Early intervention clearly attenuated increase in cardiac volume. Six months later, increases in volume were attenuated to a similar degree, depending on how soon thrombolysis had been initiated. Thus, late reperfusion produces a favorable effect on late remodeling.

Angiotensin-Converting Enzyme Inhibitors. The Studies of Left Ventricular Dysfunction (SOLVD) trial (26) studied patients with chronic congestive failure randomized to enalapril or placebo treatment, 60% of whom had had a previous myocardial infarction. Enalapril reduced both death and morbidity.

Lamas and Pfeffer (27) showed in the Survival and Ventricular Enlargement (SAVE) trial that diastolic volume barely changed with captopril treatment, whereas the volume in those who did not receive captopril increased significantly. The hearts became more spherical without capto-

pril, whereas they tended to maintain their shape in patients who did receive it. The important point is that therapy begun in the late phase of the MI (about 10 days after the acute event) and maintained over the year attenuated cardiac volume increase and remodeling. Sharpe and co-workers (28) made similar observations concerning attenuation of cardiac enlargement after MI.

Finally, survival was enhanced by angiotensin-converting-enzyme inhibition in the four-year SAVE trial (29). All-cause mortality was significantly reduced, but not until after the first 6–12 months after MI.

In the Acute Infarction Ramipril Efficacy (AIRE) trial (30), similar reductions in mortality were found, although in this trial, patients had to have been in heart failure from the MI. Here benefit was seen early on as well as late in the trial.

The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS II) (31), which used enalapril, differed from the SAVE trial in two ways. First, the drug was given intravenously within 24 hours of the infarct, whereas in SAVE it was first given on average at about 10 days. The second, and most telling, difference is that the CONSENSUS trial was stopped at about six months on the grounds that therapy had produced no benefit. It is arguable that the halt was premature because the benefits of ACE inhibition appear with long-term therapy rather than early.

Complications other than mortality included heart failure requiring hospitalization and refractory heart failure requiring the use of ACE inhibitors. In both instances, patients receiving captopril did better than those who did not. Thus, ACE inhibition reduces both mortality and the prevalence of heart failure.

An anticipated benefit was a reduction in the recurrence of myocardial infarction. In the SAVE trial, patients who received captopril had fewer infarcts at the end of four years than those who received placebo. The SOLVD trial showed similar results with enalapril.

So, in addition to the inhibition of cardiac enlargement these agents confer, there is the added benefit of improved rates of subsequent mortality and morbidity. Such benefits correlated with attenuation of LV volume rather than use of ACE inhibitors (32).

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Personal Emergency Response Systems:

Factors Associated with Use among Older Persons

DOUGLAS A. LEVINE, B.A., AND REIN TIDEIKSAAR, PH.D.

Abstract

A descriptive survey was conducted to determine factors associated with the use of personal emergency response systems among older community-residing subscribers in the New York City metropolitan area. Subscribers who wore the portable help button when alone in the home were defined as being "compliant." The average length of time the 106 respondents (average age 83 ± 9) had the system in their possession was 26 ± 18 months. Less than 50% of the subscribers were found to be fully compliant. Compliance was more common in system users who had obtained the system themselves, had a history of falls, got positive responses to activations, used an assistive mobility device, and received instruction on the system. Compliance was less common in users who had obtained the system at the request of a family member. The data suggest that disuse is a common problem that clinicians should assess regularly to assure the benefit of this intervention.

PERSONAL EMERGENCY RESPONSE SYSTEMS (PERS) are designed to provide frail older persons with the means to summon assistance in the event of an emergency, such as a fall. In its simplest form, these systems consist of three components: a help button, a base unit, and a central monitoring center. The help button is a small portable radio transmitter carried by the user and usually worn as a neck pendant. Pressing this button sends a signal to a base unit that is connected to the user's telephone, which then automatically dials a 24-hour monitoring center. This response center can determine the nature of the emergency by calling the subscriber over the telephone lines or through a two-way speaker that accompanies some systems, decreasing reliance on a telephone. Usually a neighbor or relative is called to check

on the situation or an ambulance is dispatched if a life-threatening emergency exists.

Currently, it is estimated that over 250,000 people in the United States and Canada have such a system (1). In the future, the number of older persons using these devices is likely to increase, for several reasons. First and foremost, the older population is itself getting older; the fastest-growing group in the United States is the cohort that is over 85 years old (2). By the turn of the century, this group is expected to nearly double. This population may potentially benefit most from such systems because chronic diseases and physical frailties are particularly prevalent in that group. Additionally, awareness of the availability of PERS is increasing with the proliferation of companies that market the devices, both directly to older consumers and also to home care organizations. The message conveyed to older persons is mainly the need for heightened awareness of the risk of falls and preserving safety. For home care organizations, PERS may serve as a low-cost alternative to the high cost of individual home care attendants.

The peer-reviewed literature on the use of PERS is limited and has focused mostly on stud-

From the Department of Geriatrics and Adult Development, Mount Sinai School of Medicine, New York. Presented in part at the Scientific Meeting of the American Geriatrics Society, November 1993, New Orleans, Louisiana. Supported in part by a grant from the John A. Hartford Foundation. Address reprint requests to Rein Tideiksaar, Ph.D., Department of Geriatrics and Adult Development, Box 1070, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, New York 10029

ies of the user population, technology descriptions, cost-benefit analysis, and resistance to acquiring such a system (1, 3–6). We have treated older individuals who have had a system in the home and not activated it when an emergency situation developed. Thus, this study explores potential factors that may contribute to decreased usage of PERS in the homes of older persons. Theoretically, those who subscribe to a system should be able to use it whenever they are at home alone. If the portable help button is not within reach at all times, an accident or emergency could occur and the subscriber would be unable to summon help. This is the basis for our definition of compliance. Prior good experience with the system, such as response to activations and satisfaction with the system, is likely to be associated with compliance. Additionally, the demographics of subscribers are explored in order to update the current body of knowledge. Except for anecdotal reports (4), no other studies have to our knowledge examined actual use of PERS by subscribers. A descriptive study to examine usage in a group of older persons living in the community was conducted.

Methods

The subjects of this study were recruited from six community-based personal emergency response system programs located in the New York City metropolitan area. These programs serve a large number of older individuals living in this geographical area. The programs each supplied a list of all current subscribers as of July 1, 1992. There were no substantial age, sex, or marital status differences among the subscribers. An effort was made to contact these 128 individuals by telephone to arrange a mutually convenient time for a semistructured interview. After three attempts were made to contact each subscriber, 12 (9%) were classified as unreachable. Of those contacted, 91% (106 individuals) consented to participate in the study and were subsequently interviewed. All the interviews were conducted by one investigator (DL) and most interviews were administered in the subjects' homes. Some of the subjects (22%) preferred a telephone interview.

A questionnaire was administered during the semistructured interview to elicit demographic data (age, sex, race, educational level, marital status, living situation, availability of family members), current health data (chronic diseases, functional status, physician visits), information on obtaining the system (reasons for obtaining it, length of possession, payment for it), its utiliza-

tion (the number, the reasons, and the response times for alarm activations), and compliance.

"Compliance" was defined as the user wearing the portable help button when alone in the house. Users were classified as either fully compliant, partially compliant, or noncompliant based on the portion of time alone in which the help button was worn. "Fully compliant" was defined as wearing the help button at all times while the user was alone in the home. "Partially compliant" was defined as sleeping with the help button within reach, but not wearing it at other times when alone. "Noncompliant" was defined as never wearing the button and never having it accessible.

Data analysis was performed on a Northgate Slimline 325 using SPSS/PC+. Categorical variables were analyzed by Pearson's chi-square test; continuous variables by Pearson's correlation coefficient; and continuous and categorical variables by Student's *t* test.

Results

Demographics. The demographic profile of the 106 study participants (Table 1) showed the average age of the subjects to be 82.8 ± 9.1 years, with a range from 48 to 100 years. Of the subjects, 99 (93%) were female; 88 (83%) were white; and 79 (75%) widowed. All of the subjects lived alone. Ninety-four percent had some formal education, and 71% had completed high school. Almost all of the subjects (87%) maintained regular contacts with family members, making an average of 4

TABLE 1
Demographics of Study Participants (n = 106)

	Respondents	
	No.	%
Sex		
Female	99	93.4
Male	7	6.6
Race		
White	88	83.0
African-American	12	11.3
Hispanic	6	5.7
Education		
None	6	5.7
Grade school	22	20.8
High school	37	34.9
College	38	35.8
Marital Status		
Married	2	1.9
Divorced	6	5.7
Single	19	17.9
Widowed	79	74.5

phone calls per week and 2 visits per month. There were no significant demographic differences among the subscribers from each of the six different PERS programs.

Health Status. All subjects had one or more chronic health problems. The most common conditions included hypertension, cardiovascular disease, degenerative joint disease, stroke, gait disorders, and diabetes. The subjects averaged 10.6 physician visits per year. Twenty-four percent of the participants had impairments in the activities of daily living (bathing, dressing). Assistive devices were used by 71% of the subjects (44% canes, 14% walkers, and 12% wheelchairs). Homecare services were utilized by 62% of the subjects. Fifty-two percent of the subjects had a history of one or more falls, and 60% of those falls resulted in an injury, such as a fracture or musculoskeletal sprain.

Possession of a System. Subjects had possessed a PERS for an average of 26 months ($SD \pm 18$ months) (Table 2). Subjects offered varied reasons for acquiring the system. The most common reason was the heightened level of self-assurance gained with it (43%). Other reasons included the fear of a fall (25%), vulnerability after recovering from an illness or hospitalization (14%), and the concern of family members for the individual who lives alone (9%). Over 53% of the subscribers paid for the system themselves, 35% were supported by Medicaid, and 8% had family members who provided the payments. Although the average cost was \$25 per month, 27% of the subscribers stated that the monthly fees were too expensive. There was no significant association between the subscribers' impressions of the monthly fees as being reasonable or expensive and whether or not they paid for the system themselves.

When asked how they came to obtain the system, 41% responded that a nurse or other health care worker suggested the device, 34% initiated the request themselves, and 18% obtained the device at the suggestion of a family member (Table 3).

Activation of the System. The total sample of subscribers activated their systems in an emergency an average of 0.7 times per person and 0.32 times per year. The most common reasons for ac-

TABLE 2
Summary Statistics on PERS

	Mean $\pm$ SD
Length of possession (mos)	26 $\pm$ 18
Cost (\$/mo)	25 $\pm$ 9
No. of emergency activations per year	0.32 $\pm$ 0.64

TABLE 3
Individuals Assisting in PERS Acquisition

	Respondents	
	No.	%
Health-care worker	43	41%
Self	36	34%
Family member	19	18%

tivation were falls and complaints about physical condition, such as chest pain or shortness of breath. Twenty-one percent of the individuals who activated the system in an emergency reported a less-than-satisfactory response from the monitoring center. The inadequacies reported by the users were varied. Some complained that the response time was too slow or that the operators from the companies were impolite. Others related that their particular situation was deemed to be less emergent than the caller believed and it was suggested that a neighbor or relative be summoned instead of emergency medical services.

Compliance. Among the respondents, 45% were fully compliant, 27% were partially compliant, and 27% were noncompliant. Several factors were positively associated with compliance (Fig.). Those who obtained the device of their own accord were more likely to be compliant than those who obtained it at the suggestion of a family member or the recommendation of a health care worker ($p 0.04$). In addition, those who were at risk for falls were more compliant than those who were not ($p 0.04$). Furthermore, subscribers who received instruction on the operation and use of the system, as well as those who had got a positive response during a previous emergency situation, were more compliant ($p 0.03$ and 0.01 , respectively). Older persons who used an assistive mobility device were more likely to wear the help button ($p 0.02$). Education level, length of system possession, number of emergency activations, cost borne by the individual, and frequency of physician visits were not significantly associated with compliance.

Those individuals who had obtained a PERS at the suggestion of a family member were less likely to be compliant than those who made the decision themselves ($p 0.04$). Lastly, respondents who were not satisfied with the PERS were also less likely to have routinely worn the portable transmitter ($p 0.001$).

Discussion

The benefits gained by PERS can be divided into three distinct categories: benefits to the user

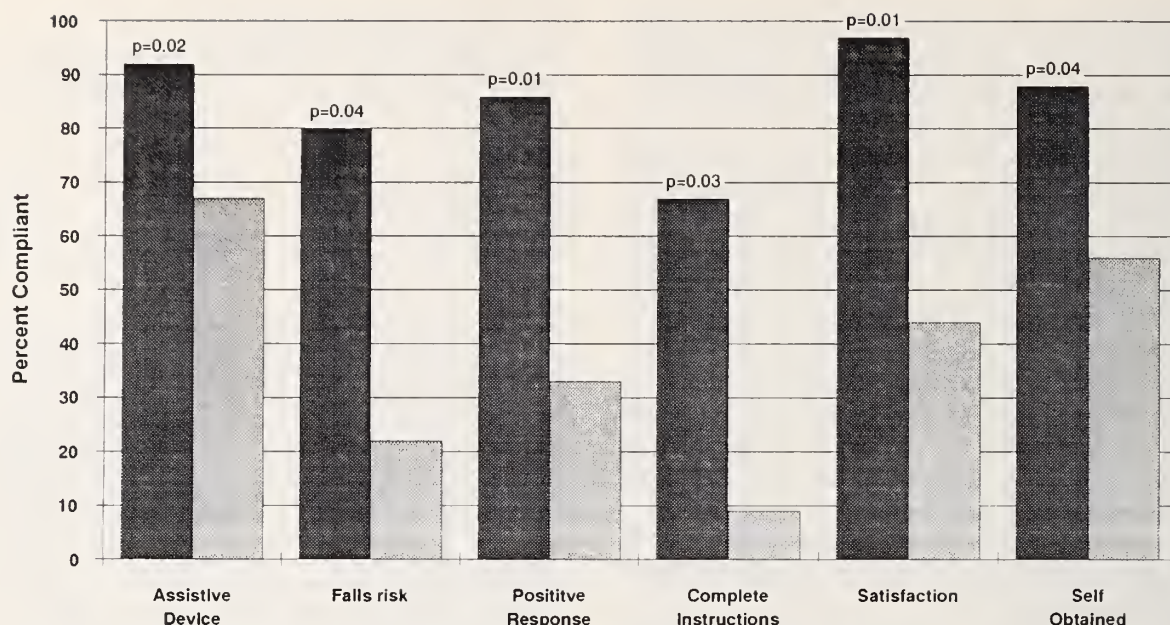


Fig. Factors associated with the use of personal emergency response systems. Respondents characterized by any one of six statistically significant variables—use of an assistive mobility device, risk of falls, prior positive response to system activations, having received complete operating instructions, overall satisfaction with the system, and having obtained the system independently—were more likely to be compliant than those who did not. Black bars, percentage of users compliant when the particular variable was present; gray bars, percentage of users compliant when the particular variable was not present.

or subscriber, benefits to the family caregiver, and benefits to the health care system. With respect to each of these, the limited prior literature concerning PERS utilization has been positive. For the older person there are a number of psychological benefits: a heightened feeling of security, reduced fear of falling, and increased autonomy or independence (1, 3, 7). For the family member, benefits include reduced anxiety about the safety of the older person, and financial savings, because the cost of the system is about \$1 per day, much less than paying for home attendants to provide sentry duty (5, 7). For the health-care system, PERS has been found to have a low cost-benefit ratio. Ruchlin and Morris demonstrated that community-residing elderly who subscribed to a system used fewer medical and social support resources (6) and concluded that the cost-beneficial merits of these systems warrant their consideration as a component of programs targeted toward the elderly. However, the potential advantages of PERS can only be recognized if the older subscriber is compliant with the system.

The primary objective of this study was to determine the level of use of PERS. This study population was similar to study subjects in other published reports in regard to age, sex, living situation, health status, and level of functioning (1, 6, 7). As in previous anecdotal reports, usage was greater in those individuals with a history of falls (7). System usage was enhanced if the older per-

son obtained it themselves, received proper instructions, and got positive and timely responses during emergency activations. These findings have not been previously described. In addition, older persons who used an assistive mobility device (cane, walker, wheelchair) were found more likely to wear the portable help button. Assuming that persons who require a mobility device are more functionally impaired, this finding supports the work of Dibner, who found that PERS acceptance was associated with increasing levels of disability (1).

Of greater significance, 54% of this study population were not using the system fully. This was unexpected, because the majority of published reports have shown older persons to be compliant and satisfied with their PERS (4). A few studies have demonstrated initial refusal to obtain a system, often because of such host-related factors as fear of technology, cost, or privacy invasion (3, 4). However, data on the prevalence of disuse in older persons already subscribing to such a system have not been previously reported. As a result, these findings on reasons for disuse are pertinent.

In this population, disuse was associated with obtaining the device through others, such as a family member, or having had poor responses to prior activations. The former is most likely related to issues of personal autonomy and the latter to a negatively conditioned response. Another

factor that could have influenced disuse is the issue of cognitive impairment and level of understanding among the study population. Although we did not perform mental status tests, the subjects were believed to be cognitively intact because the information they supplied during the interviews correlated with their medical records. Additionally, aside from these host-related factors, systemwide elements may account for the disuse among these subscribers. Unsatisfactory service (inadequate response time, impolite operators, for example) may lead subscribers who would otherwise be compliant to disregard the proper operating protocols for the device.

Although this study did not examine the reasons for the continued retention of systems by subjects who did not use the device, interviews with the subjects suggest several logical reasons. There are particular factors specific to these individuals that may cause unutilized systems to be retained. Many subscribers have the costs of the system covered by either a family member or Medicaid. In these situations, it may require more effort to discontinue the service than to allow the device to remain unused. Dibner et al. found that persons who were accepting of systems were also agreeable to other services (4). However, whether persons in that study were actually using the systems is not entirely clear. Thus, some Medicaid recipients may feel that other services they are receiving may be withdrawn should they refuse the PERS. Furthermore, although the noncompliant subscribers are not actually benefiting from their systems, they may perceive an added sense of security by having the device nearby. This study was unable to analyze the characteristics of individuals who had been but were no longer subscribers because names of those individuals were not available.

The level of disuse discovered through this study is potentially dangerous. As with any medical intervention, whether medication regimen or home safety device, if individuals are noncompliant serious adverse effects may occur. In this case, falls may go unnoticed, leading to increased post-fall lie time and accompanying sequelae. In addition, these subjects may be at risk for disuse of other services which deserve further investigation. Additionally, it is now clear that assumptions on PERS usage should not be based simply on possession or payment for such a device.

Conclusions. Even though PERS have been shown to have a low cost-benefit ratio and to increase sense of security and offer independence (1,

3, 6, 7), potential subscriber disuse must be examined to prevent associated complications. At present there are unutilized systems in place that are not only resulting in excess third-party payor costs but—more important—are not providing the intended benefits. As this technology continues to expand, awareness of factors associated with increased use is important. This study has identified the breadth of previously undetermined disuse in PERS subscribers, as well as some of the factors responsible. Many of these factors, such as inadequate instructions and system dissatisfaction, are readily apparent and often modifiable. Therefore, clinicians should assess system use and evaluate disuse regularly, as they would assess compliance with any other medical regimen.

Future research needs to include a more geographically varied sample in order to explore the extent of disuse nationwide as well as provide longitudinal follow-up. Additionally, the consequences of disuse, both partial and complete, need to be fully examined. Finally, interventions that could improve usage should also be explored.

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Increase in Leukocyte Adhesiveness and Aggregation with Stress:

A Model of Human Congestive Heart Failure

JONATHAN M. SCHAPIRO, MD, LIMOR ARBER, DDS, DINA LEV, MD, DOV WEKSLER, MD, ELIEZER LIBERMAN, MD, ASHER WINDER, MD, SHLOMO BERLINER, MD PhD, AND NADIR ARBER, MD.

Abstract

Stress has a significant influence on the function of the human organism. A simple, rapid, inexpensive, and reliable marker for stress would therefore be of great value. We have recently noted that stress increases the state of leukocyte adhesiveness and aggregation in the peripheral blood. We evaluated 64 patients who had various degrees of congestive heart failure, a condition known to induce a state of physiologic stress, to verify whether a relation exists between the intensity of the stress response and the magnitude of leukocyte adhesiveness. Included in the 64 were 53 patients without congestive heart failure, 23 with compensated failure, 22 with significant congestive heart failure, and 19 with florid pulmonary edema. The percentage of aggregated leukocytes in these four groups was $6\% \pm 4\%$, $6\% \pm 4\%$, $10.5\% \pm 5\%$, and $15\% \pm 14\%$. Values for the third and fourth group differed in a statistically significant way. Thus, with further investigation into additional stress-inducing conditions, the state of leukocyte adhesion and aggregation may prove to be a reliable marker for the detection of stress and an inexpensive tool for quantifying its severity.

STRESS has significant effects on the function of the human organism (1). A simple, rapid, inexpensive, and reliable marker of stress might, therefore, be of value in clinical and investigational medicine. We have recently reported that stress is associated with an increment in the state of leukocyte adhesiveness and aggregation (LAA) in the peripheral blood (2–6). The main point of the study we report here was to determine whether a relation exists between the degree of stress reaction and increase in LAA. Congestive heart failure (CHF) is a common condition inducing a state of stress manifested by typical hormonal and neural responses. It is not clear whether mental stress is associated with the same hormonal and neural responses that occur in CHF. Patients

with CHF can be categorized by functional class, allowing for grading of the severity of the condition. We therefore chose to study the state of LAA in patients with CHF as a model of a quantifiable state of stress. Our results point to the possibility that the LAA reaction relates to the severity of stress.

Patients and Methods

The study included patients with ischemic heart diseases (anginal syndrome, history of myocardial infarction, or history of ischemic heart disease documented by a previous coronary angiography) who came to the Emergency Room with complaints of chest pain or CHF signs and symptoms.

The study excluded patients with fever, respiratory tract infection, or other underlying inflammatory conditions that could themselves induce an increased LAA. Patients were classified as having definite CHF if they had two major or one major and two minor criteria of CHF. In this

From the Department of Internal Medicine D, Beilinson Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Israel. Address reprint requests to Nadir Arber, M.D., Department of Gastroenterology, Tel Aviv Medical Center, 6 Weizman Street, Tel Aviv 64239, Israel.

study, major criteria of CHF included paroxysmal nocturnal dyspnea or orthopnea, neck-vein distention, rales, cardiomegaly, acute pulmonary edema, S_3 gallop, and hepatjugular reflux; minor criteria included ankle edema, night cough, dyspnea on exertion, hepatomegaly, pleural effusion, and tachycardia.

Patients were classified by a skilled cardiologist as either no CHF, compensated CHF, significant CHF, or florid pulmonary edema in relation to their respective class I–IV New York Heart Association functional classification. Posterior-anterior chest roentgenograms of patients who had the roentgenograms on the day of the LAA test were classified by a skilled diagnostic roentgenologist who was unaware of the results of the laboratory data as showing either a normal chest x-ray, mild to moderate CHF, or pulmonary edema. The white blood cell count and differential count were performed by Technicon H1 Autoanalyzer and the state of LAA determined by direct slide test (7).

Direct Slide Test. For the test, blood is drawn into a syringe that contains sodium citrate (one volume of 3.8% citrate and three volumes of whole blood). Several large drops of blood are placed on a slide held for 2–3 sec at an angle of 45° , so that the blood can slip down by gravity, leaving a fine film of blood. The slides are then dried while in a horizontal position in an incubator or at room temperature. To cause hemolysis the dried slides are placed at -18°C for 10 min. Fixation is performed with absolute methanol, and staining with hematoxylin. For microscopic examination, a drop of immersion oil is placed on the stained slide and covered with a cover glass. The $\times 1,000$ ocular is employed for the examination. Because of the relative thickness of the blood film, not all the leukocytes are present on the same level, and the focus has to be adjusted often during the examination.

The percentage of aggregated leukocytes on the slides is determined by counting 300 white blood cells at random (for example, if 30 of 300 are in aggregates, whether one aggregate of 30 cells or two aggregates of 15, the percentage of aggregated leukocytes is 10%). Cells are considered aggregated when three or more nuclei less than one cell diameter apart are seen.

For each patient two slides are prepared, and the final result is a simple mean of both. Variation between duplicates does not generally exceed 20%, although from time to time larger differences are seen due to nonhomogeneous distribution of the aggregates. This is also the variation

noted when two independent observers examine different slides from the same patient. When the same slide is tested and retested, differences do not exceed 15%.

The intra-assay coefficient of variation was calculated from 15 slides that were simultaneously prepared from the same donor (value 0.2), and the interassay coefficient of variation was calculated when the same normal donor was examined on successive days for 15 consecutive days (value 0.3). The composition of the aggregates is generally similar to the differential white blood cell count, that is, it is formed mainly of neutrophils in cases of neutrophilia and of lymphocytes in cases of lymphocytosis. Mixed aggregates of polymorphonuclear and mononuclear leukocytes are often seen. If incubation is used for drying, results of the test can be given within 30 min. The percentage of polymorphonuclears and lympho-

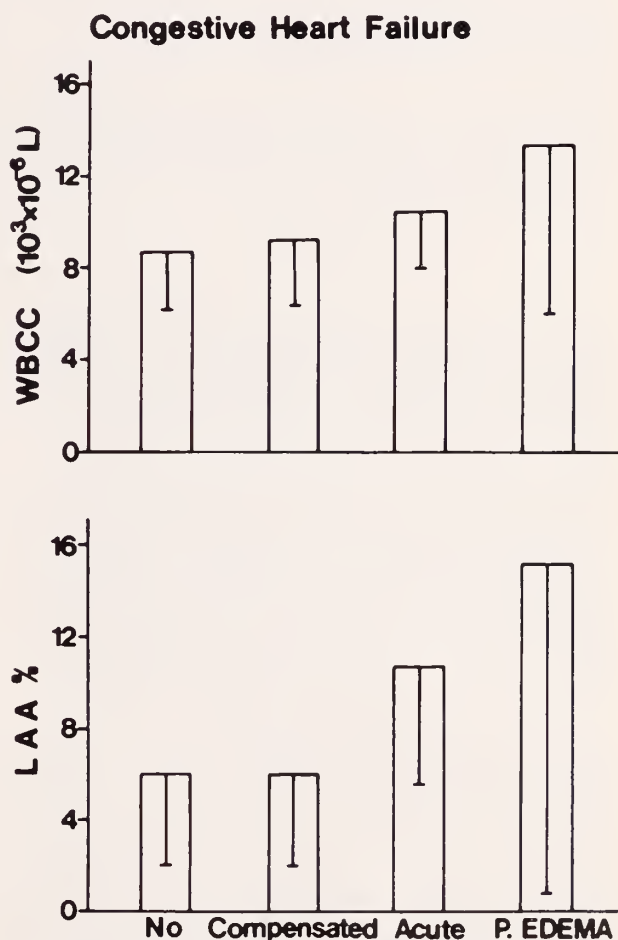


Fig. Mean $\pm$ SD values for white blood cell count (WBC) and state of leukocyte adhesiveness and aggregation (LAA) in the peripheral blood in patients with various degrees of congestive heart failure (CHF). Assuming that the stress response is proportional to the severity of CHF, one can see a parallel increment between the severity of the CHF and the LAA response.

TABLE
Laboratory Values in Patients Who Had Chest X-Rays

	No CHF	Mild to moderate CHF	Pulmonary edema
WBC (cells/ 10^{-6} /L)	8354 $\pm$ 2725 [†] n = 24	10125 $\pm$ 2763 [†] n = 24	11937 $\pm$ 5319* n = 10
PPMN (%)	68 $\pm$ 13 n = 16	74 $\pm$ 11.6 n = 15	75 $\pm$ 10 n = 7
PLY (%)	21 $\pm$ 11 n = 16	17.5 $\pm$ 10 n = 15	16 $\pm$ 10 n = 7
LAA (%)	6.2 $\pm$ 4.4 [†] n = 27	8.8 $\pm$ 4.7 [†] n = 30	13.2 $\pm$ 11* n = 13
PMN (%)	66 $\pm$ 12 n = 20	69 $\pm$ 15 n = 24	73 $\pm$ 11 n = 12
LY (%)	28 $\pm$ 12 n = 20	25 $\pm$ 15 n = 24	25 $\pm$ 12 n = 12

CHF, congestive heart failure; WBC, white blood cell count; PPMN, percentage of polymorphonuclears in the peripheral routine differential count; PLY, percentage of lymphocytes in peripheral routine differential count; LAA, leukocyte adhesiveness/aggregation; PMN, percentage of polymorphonuclears in aggregates; LY, percentage of lymphocytes in aggregates.

* $P < 0.05$.

[†] $P < 0.05$.

cytes in the aggregates was determined on 100 cells present in aggregates.

For the statistical analysis we used the SPSS (SPSS Inc., 444 N. Michigan Ave., Chicago, Ill.) package, which includes the paired *t*-test as well as the Pearson coefficient of correlation. Results are reported as mean $\pm$ SD.

Results

A total of 117 patients (74 men, 46 women) aged 70 ± 14 years were examined and classified as either no CHF (53), compensated CHF (23), significant CHF (22), or pulmonary edema (19); their respected LAA values being 6 ± 4 , 6 ± 4 , 10.5 ± 5 and $15 \pm 14\%$. The differences between the significant CHF and the no CHF group were significant at $p = 0.001$ and differences between the pulmonary edema and the no CHF groups were significant at $p 0.02$. Increased LAA values paralleled the increment in the white blood cell count (WBC) (Fig.). The correlation between both variables was significant ($r 0.82$, $p < 0.0001$).

Similar results were obtained when we analyzed the data by result of chest x-rays (Table). There is a significant (<0.05) increment in WBC and LAA in the group with mild to moderate CHF as well as the group with pulmonary edema in comparison to the no-CHF group. The percentage of polymorphonuclears and lymphocytes in the peripheral differential count correlated significantly ($r 0.8$, $p < 0.0001$) with that found in the aggregates.

Nineteen patients had myocardial ischemia and seven developed a myocardial infarction.

Laboratory data did not change significantly after excluding these patients, compatible with our recent observations that neither myocardial ischemia nor myocardial infarction during its first hours induces high LAA values (8).

Discussion

The study reported here demonstrates that apart from the leukocytotic reaction, severe CHF is also accompanied by an increment in the state of leukocyte adhesiveness and aggregation in the peripheral blood. Activation of the neurohumoral system during heart failure has been shown to occur (9), and its intensity has been related to the degree of failure. We therefore studied a group of CHF patients to determine whether the degree of LAA in the peripheral blood significantly correlates with the intensity of CHF-related stress.

Since there are no conventional biochemical markers for determination of degree of stress, one has to rely on classifications that would be acceptable clinically. We believe the categories of CHF to be one such classification, since it is obvious that the degree of neurohumoral activation and the accompanying stress increase from patients identified as NYHA functional class I to those identified as in progressive higher classes. The substantial finding of the present study is therefore the increased LAA found in patients with severe CHF, which is an obviously stressful condition. The LAA test cannot discriminate between mental or physical stress; LAA has been shown by us in the past (2–6, 10) to appear following both mental and physical stress.

The mechanism of the increased LAA response during stress is not known. Several humoral factors released during stress could be associated with leukocyte aggregation (11, 12), and the increased tumor necrosis factor levels in patients with CHF (13) could be a contributory factor. Apart from being a stress marker, increased leukocyte "stickiness" could be relevant to CHF because (a) sticky polymorphonuclears could contribute to capillary flow retardation (14), which might be detrimental in the face of a vasoconstricted periphery; and (b) increased adhesiveness could contribute to pulmonary leukostasis and damage to the endothelium of the pulmonary vasculature (15), a detrimental event in the presence of hypoxemia, pulmonary hypertension, and capillary leak.

We conclude that CHF is associated with an increased LAA response. The study reported here shows that the degree of LAA response is related to the intensity of stress, which increases with progressively more severe CHF. Yet further studies of LAA in additional stress-inducing conditions are needed to confirm this finding.

Finally, it is conceivable that examination of the peripheral blood might not detect the extent of leukocyte adhesiveness, since most sticky leukocytes might be trapped in the tissues. In any case, research on leukocyte adhesiveness in CHF is not a theoretical issue in light of potential antiadhesive therapies that have been shown to prevent neutrophil-mediated pulmonary vascular endothelial injury (15).

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Lipomatosis of the Ileocecal Valve Leading to Episodes of Partial Small Bowel Obstruction

BASIL J. MYLONAKIS, M.D., GRIGORIOS G. KARKANIAS, M.D., VANGELOGIANNIS A. KATERGIANNAKIS, M.D.,
ANDREAS J. MANOURAS, M.D., AND NICHOLAS S. APOSTOLIDIS, M.D., FACS

Abstract

The cases of two female patients with lipomatosis of the ileocecal valve inducing episodes of intestinal obstruction are presented. A barium enema with air contrast was performed in patient 1; patient 2 was operated on to treat ileus. Resection of the fatty tissue from the ileocecal valve was performed at operation, after histologic diagnosis on frozen section. These cases suggest that limited resection removing fatty tissue is effective and preferable to more radical resection.

Ileocecal valve lipomatosis or lipohyperplasia is a lesion characterized by diffuse annular infiltration of fatty tissue, mainly in the submucous layer, resulting in a symmetric deformation of the valve and possibly narrowing the lumen of the cecum. Many patients who have lipomatosis of the ileocecal valve are asymptomatic or have only insignificant symptoms (1).

We present two patients with lipomatosis of the ileocecal valve. One patient had diffuse abdominal colicky pain, and a filling defect in the cecum was found on barium enema examination. The other patient underwent an emergency laparotomy because of intestinal obstruction.

Case Reports

Case 1. A 51-year-old woman had a seven-month history of diffuse abdominal colic pain and episodes of diarrhea. She was dehydrated, and the

pain was mainly referred to the epigastrium and the right upper abdominal quadrant. After initial conservative treatment by intravenous administration of fluids and electrolytes, the patient underwent a barium enema with air contrast that revealed a constant regular filling defect of the area of the ascending colon; the appendix could not be visualized (Fig. 1). This defect appeared to be a nonpedunculated polyp prolapsing into the colon. A colonoscopy that was successful up to the hepatic flexure showed normal large bowel mucosa. A subsequent abdominal CT scan demonstrated a mass, possibly a polyp of the ileocecal valve.

The patient was referred for surgery. At laparotomy a cecotomy was performed and the suspicion of lipomatosis of the ileocecal valve was raised. Frozen section of multiple biopsy specimens revealed lipomatosis. Resection of the adipose tissue from the ileocecal valve was performed. The postoperative course was uneventful, and the patient left the hospital after nine days. She is doing well four years later.

Histologic examination revealed mucosa with moderate chronic inflammation and a submucous layer whose appearance was consistent with lipomatosis of the ileocecal valve (Figs. 2, 3).

From the First Propaedeutic Surgical Clinic, University of Athens Medical School, Hippocraton Hospital, Athens, Greece. Address correspondence and reprint requests to Grigorios Karkanias, M.D., Kyprion Agoniston 30, GR-16451 Argyrupolis, Athens, Greece.



Fig. 1. Case 1: barium enema in two views is evidence of a rounded, smoothly outlined filling defect in ascending colon.



Fig. 2. Case 2: abundant mature fatty tissue in submucosal layer (H-E original magnification $\times 125$).



Fig. 3. Case 1: mature fatty tissue, muscularis mucosae including lymph node and bed of mucosal crypts (H-E original magnification $\times 250$).

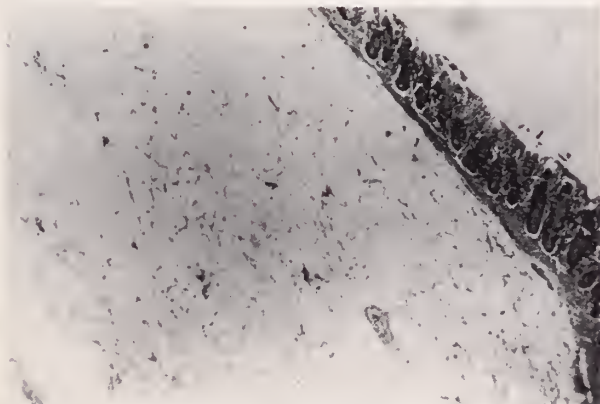


Fig. 4. Case 2: presence of abundant fatty tissue in submucosal layer (H-E original magnification $\times 125$).

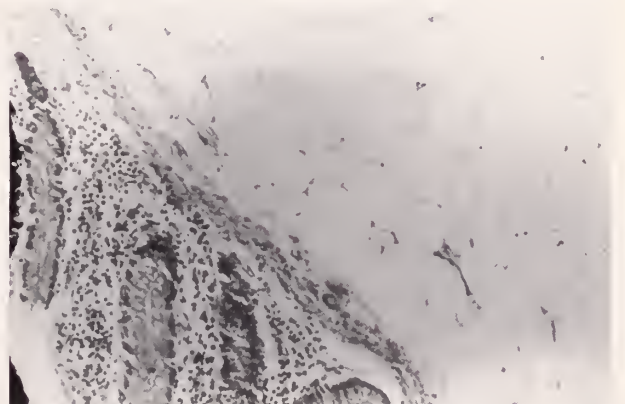


Fig. 5. Case 2: fatty tissue cells in submucosal layer and thick muscularis mucosae (H-E original magnification $\times 250$).

Case 2. A 60-year-old woman reported a five-year history of diffuse abdominal pain. During the prior two years she had been hospitalized with recurrent small bowel obstruction. She had undergone a hysterectomy 12 years earlier, secondary to fibromatosis of the uterus. The patient was admitted with symptoms of ileus and multiple small bowel air-fluid levels. Under conservative treatment, her condition became worse, and an operation was performed.

At laparotomy the whole small bowel was dilated. Multiple enteric and parietal peritoneum adhesions were found, but they were not deemed to be the main cause of intestinal obstruction. On inspection of the bowel, a round mass that did not suggest malignancy was palpated at the ileocecal valve. A colotomy was performed, and multiple biopsies were obtained. Frozen section showed the presence of lipomatosis. The lesion was resected and the patient was discharged 10 days later. She has no signs of intestinal obstruction during a 40-month postoperative follow-up.

Histologic examination revealed increased adipose tissue in the submucosa and thickness of the muscularis mucosae (Figs. 4, 5).

Discussion

Lipomatosis of the ileocecal valve is the most common cause of prominent or enlarged ileocecal valve (2, 3). It is more common than was previously thought, and a statistically significant correlation between the degree of ileocecal valve lipohyperplasia and the degree of cardiac right ventricular fatty infiltration, pancreatic fatty infiltration, and a total body weight has been described (4, 5). Lipomatosis is differentiated from the rare true lipomas based on the lack of encapsulation (6). It is more common in women over the age of 40 (2).

The common symptoms of ileocecal valve lipomatosis are abdominal pain, abdominal distention, nausea, vomiting, diarrhea, and constipation. A case of lipomatosis of the ileocecal valve

simulating Crohn's disease has been reported (7). In the two patients we report here, colic, abdominal pain, and intestinal obstruction were the symptoms.

The differential diagnoses considered included a polyp, a benign tumor, a carcinoma, and adhesions. Barium enema examination may not be helpful in differentiating these possibilities; it was not definitive in case 1 (7). Colonoscopy may be more helpful because it offers the possibility of obtaining biopsy specimens for histologic examination. Unfortunately, in case 1 the colonoscope did not reach the lesion. This examination was not performed in case 2, because preoperatively adhesions were regarded as the cause of the obstruction.

Limited resection of ileum and cecum that removes adipose tissue from the ileocecal valve is considered an effective treatment (8). Radical resections must be avoided (3, 6, 7).

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Translumbar Amputation:

The Longest Survivor—A Case Update

ALEXANDER RANALD MACKENZIE, CH.M., M.D., FACS

Abstract

Background: Translumbar amputation, known also as hemicorporectomy, was first described by Kredel but was not performed until 10 years later in 1960. It appears that 44 such operations have been reported but probably several others remain unpublished.

Methods: The operation has been performed in 44 reported patients over the past 30 years in more or less the same fashion. Most have been done as a one-stage procedure, but the author favors laparotomy and maturation of urinary and fecal diversions before doing the amputation about two weeks later.

Results: Overhydration caused the death of the first three patients. This problem was avoided in the Memorial Sloan-Kettering patients by careful monitoring of central venous pressure. There were no operative deaths, but 8 of the 44 patients died within a month. Survival of cancer patients has not been good, but those with benign lesions have survived fairly well.

Conclusion: This case is remarkable in that, despite a rapidly advancing cancer of the bladder, the patient lived for over 28 years. It is gratifying to see that other surgeons and patients have not abandoned this most radical of all operations when no other therapy can preserve life.

FREDERICK E. KREDEL should be considered the father of translumbar amputation. Using the term "halfectomy," he performed the procedure on a cadaver in 1950. He demonstrated the slide and advocated the operation for otherwise untreatable pelvic cancer at a meeting in February 1951 (1). Later that year he completed the first stage of a projected two-stage operative hemicorporectomy on a patient who had locally invasive pelvic cancer. After the initial stage, the patient refused further surgery (2).

The first complete operation was performed by Kennedy in Detroit in 1960 (3). The patient was 74 years old and suffered from locally advanced rectal cancer. The operation, done in one stage, was completed in 13 hours. The patient died from pulmonary edema 10 days later.

The second translumbar amputation was per-

formed in 1961 by Aust (4). The patient was a 29-year-old male paraplegic who developed epidermoid cancer in a decubitus ulcer. The operation was done in two stages, the second part occupying 6½ hours. The patient succumbed to overhydration during treatment for heat stroke 19 years later (5).

The third patient had locally advanced cancer of the cervix. She died from pulmonary edema four days later (6).

Three of the next four subjects of this operation were men who had advanced urologic cancer.

Case Report

On February 19, 1964, the patient underwent what was at that time the most extensive surgical procedure undertaken by the Urologic Service of Memorial Sloan-Kettering Cancer Center. His operation is described as one in a series of 9 pubic bone resections (7). The surgical specimen, removed in one piece, consisted of pelvic peritoneum and lymph nodes, rectum and anus, bladder, prostate, penis, all four pubic rami, and a

From the Urologic Section, Department of Surgery, Long Beach Medical Center, Long Beach, NY. Address reprint requests to A. R. Mackenzie, 51 Mineola Avenue, Point Lookout, NY 11569.

full-thickness inverted-V-shaped portion of abdominal wall extending up to the umbilicus. The defect was closed with Marlex mesh covered by the skin of the penis, which was flayed from the corpus spongiosum and corpora cavernosa. Diversions were via a sigmoid urinary conduit and a terminal colostomy.

The operation for bladder cancer was considered curative, but by late August 1964 there was a massive recurrence occupying the entire pelvis, grossly exophytic in the perineum (8). Laparotomy on September 4 was undertaken for the purpose of evaluating the possibility of translumbar amputation. The patient was deteriorating, partly because of a loop of small bowel adherent to the recurrent tumor, resulting in intermittent obstruction.

It was apparent that the tumor could be removed in toto by translumbar amputation. I presented the case at the joint New York Hospital-Memorial Hospital urologic conference, which was attended by a large number of urologists and trainees. A poll of all present showed that none supported the proposed operation (9). I therefore discussed the case with Dr. Theodore Miller, chief of the Bone Service of Memorial Hospital. He accepted the patient, and we performed the operation on September 23, 1964.

The patient had a smooth recovery and was rehabilitated to the extent of walking with crutches and driving a car. At home he preferred to move around in a wheelchair.

I visited him and communicated with him over the years because he objected to driving two hours to my office.

Before the operation he expressed a desire to see his two preteen boys grow to manhood. He lived to see several grandchildren. At no time did he or his wife and sons express regret that the operation had been done. My visits showed me a contented, happy home and appreciation and respect for my unpopular decision. He compared his life favorably with that of a cousin who was permanently tetraplegic on wakening from a cervical disc operation.

On February 21, 1993, his wife called me to say he had died in a hospital the previous day, the cause being a bowel obstruction for which he refused operation.

He died aged 77, having survived 28 years and 5 months after translumbar amputation.

Discussion

To date, as far as I can tell, 44 translumbar amputations have been performed. Ferrara (2)

summarized 38 cases but failed to include 6 others that were reported (10) shortly before his paper was accepted for publication. There have been no operative deaths, but 8 patients died within one month of operation, including one of the 11 patients operated on in Memorial Hospital.

I strongly recommend that the urinary and fecal diversions be performed at least two weeks before amputation. The one-stage operation is long and arduous and is fraught with the possibility of serious complications. For example, Terz et al. (10) reported major complications in five of their patients, including two urinary fistulas, a small-bowel fistula, a small-bowel obstruction, internal bleeding, and separation of the incision. All of his six cases occupied many hours of operating and the patients sustained extensive loss of blood. Once the diversions are established, the amputation can be accomplished in two hours (11).

My preference for the two-stage operation is based on an unpublished study I conducted in the 1960s on over 1200 urologic patients who had ureteroenterostomies as part of major cancer operations in Memorial Sloan-Kettering Cancer Center, most of them radical cystectomies for bladder cancer. There were 27 small-bowel fistulas, 42 large-bowel fistulas, and 61 urinary fistulas. Apart from the formidable morbidity these complications entail, mortality rates were 85%, 24%, and 34%, respectively.

Another advantage of preliminary diversions is the opportunity to assess operability. In the urologic and gynecologic cases in which I was involved, all patients had preliminary laparotomy for the purpose of removing the tumor in a conventional fashion or determining if translumbar removal offered an opportunity for cure. All had urinary and fecal diversions created at laparotomy, or—in the subject of this report—six months earlier. I still maintain that the two-stage procedure is the preferred approach; it establishes the feasibility of amputation, although nowadays computerized tomography and magnetic resonance imaging may be of additional or even alternative value. Theodore Miller has performed several one-stage translumbar amputations that did not involve the complications cited above, but such operations are invariably long and arduous and involve greater loss of blood than the two-stage procedures. The avoidance of concurrent opening of the alimentary tract and the dural space is obvious and, it is to be hoped, allows some mitigation of those elements of the operation that are criticized as ethically questionable.

In 1968, translumbar amputation was de-

scribed as the most revolutionary of all operations (12). Not all surgeons are prepared psychologically to undertake the procedure, and even fewer patients will accept it as an alternative to fairly imminent death. Over a period of three or four years my colleagues on the urologic, gynecologic, and rectal services of Memorial Sloan-Kettering Cancer Center referred approximately 50 patients to me for the operation, only 5 of whom agreed to have it. Of those 5 patients, 4 underwent amputation. The fifth (13) elected to have a trial of chemotherapy and X-ray therapy for rhabdomyosarcoma of the bladder; he enjoyed a remission of about three years before reaching the stage where amputation, which he at that point accepted, was no longer possible. Three of the 4 amputees died from metastases within a year. Of the approximately 50 candidates referred to me, all had been adequately evaluated by the referring services, and to my knowledge their survival was invariably short.

Theodore Miller's patients, who generally had osseous tumors, benign and malignant, were referred from all over the world or were paraplegics salvaged from veterans' hospitals, which provoked bureaucratic displeasure (personal communication from T. Miller). The acceptance rate was similar to mine. Some of his patients may still be alive and may eventually surpass the length of survival of the patient herein described, as may patients operated on in other countries with disorders of traumatic or nontraumatic origin.

The most comprehensive studies are those reported by Ferrara (2), (38 cases) and by Terz et al. (6 cases).

Conclusions

It is gratifying that others have continued to utilize this "revolutionary" operation up to the

present. The survival of this patient, regarded at the time as a highly unfavorable candidate, for over 28 years should encourage consideration of translumbar amputation as a last resort under patently obvious circumstances for those unfortunate patients whose courage far exceeds that necessary in the willing and capable surgeon.

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Massive Hemorrhage from Solitary Rectal Ulcer:

Toward a Definitive Treatment

SANDER R. BINDEROW, M.D., RAOUL MAYER, M.D., PH.D., AND JEFFREY S. FREED, M.D., F.A.C.G.

Abstract

Two recent cases of massive bleeding from a solitary rectal ulcer which occurred in patients at The Mount Sinai Hospital are presented. This unusual complication of a poorly understood condition has been treated in the past by a variety of medical and surgical approaches; no consensus has been reached. In both cases an abdominal rectosigmoid resection was ultimately performed after local control and diversion were unsuccessful. A review of the literature and a discussion of this new approach are presented.

SOLITARY RECTAL ULCER is an uncommon condition with an interesting and poorly understood pathogenesis (1–3). The ulcer as a cause of massive lower gastrointestinal bleeding requiring multiple transfusions has been reported only sporadically (1, 2, 4, 8). Of these cases, only five have necessitated emergent, major surgical intervention (4, 5, 7). We report two cases of benign rectal ulcer causing massive hemorrhage which required transabdominal resection of the rectum after an unsuccessful attempt at local control. A discussion of the two cases and comparison of the surgery performed with the previously reported surgical options are presented in an effort to determine the most appropriate treatment for this unusual condition.

Case Reports

Case 1. A 68-year-old woman with hemodialysis-dependent renal failure was admitted after a traumatic right hip fracture. Initial laboratory values included hematocrit 33%, hemoglobin

11.6 mg/dL, blood urea nitrogen 17 mg/dL, and creatinine 11.6 mg/dL. The prothrombin and partial thromboplastin times were normal. An uneventful repair of the right hip fracture with bipolar prosthesis was performed.

Ten days postoperatively, the patient experienced an episode of bright red blood per rectum with associated hypotension, tachycardia, and a fall in hematocrit from 34% to 25%. Intravenous fluid resuscitation and blood transfusion were begun. Placement of a nasogastric tube returned bilious material without blood. Rigid sigmoidoscopy at the bedside was nondiagnostic due to copious bloody stool. The patient's condition stabilized with cessation of bleeding after a total of seven units of packed red blood cells had been transfused. Subsequent elective colonoscopy after bowel lavage revealed a rectal ulcer on the posterior wall of the rectum at 7 cm from the anal verge that was not actively bleeding. No other pathologic condition was identified.

Five days after the initial episode, red blood was again passed per rectum, accompanied by hypotension and a seven-point fall in hematocrit. Rigid sigmoidoscopy revealed bleeding from the rectal ulcer. The patient underwent emergency hemodialysis and was brought to the operating room.

With the patient under general anesthesia,

anoscopy showed a 4-cm actively bleeding superficial ulceration beginning 5 cm from the anal verge. After many biopsies were taken, electrofulguration was applied until bleeding ceased. A loop sigmoid colostomy was then created through a left lower quadrant incision.

The initial postoperative course was uneventful; the patient's hematocrit was stable and the colostomy functioning. However, one week after the procedure the patient again developed bright red rectal bleeding. The patient returned to the operating room, where an abdominal rectosigmoidectomy was performed. On opening the specimen, the entire ulcer was present just proximal to the rectal resection margin. The loop colostomy was converted to an end type, and the anal cuff was left open for drainage.

Case 2. A 74-year-old woman with a coin lesion of the right upper lobe of the lung was admitted for treatment on October 28, 1992. The patient had had mitral valve replacement in 1975 and again in 1981. Pulmonary hypertension persisted after the second valve replacement. Laboratory test results were normal except for elevated carcinoembryonic antigen of 12 $\mu\text{g/L}$. The patient did not have a history of gastrointestinal disease or lower gastrointestinal bleeding.

On October 29, the patient underwent a right upper lobectomy. Swan-Ganz monitoring confirmed pulmonary hypertension. Because of excessive bleeding in the immediate postoperative period, she was returned to the operating room, where an injury to the right pulmonary artery was repaired, controlling the bleeding.

The patient required ventilatory support and several courses of antibiotics for pulmonary infection. On November 26, 1992, massive bright red rectal bleeding was noted. A flexible sigmoidoscopy was performed, revealing a giant posterolateral rectal ulcer approximately 5 cm from the anal verge extending proximally 4 cm. Because of continued bleeding, the patient underwent examination under anesthesia and suture ligation of multiple sites of hemorrhage. This controlled the bleeding at that time.

Seven days later, unexpected massive rectal bleeding recurred. It was decided that more definitive therapy was necessary. At laparotomy, a rectosigmoidectomy with end colostomy was performed, including the rectal ulcer; a 3-cm anal stump was left open for drainage.

The patient survived 94 days after this last procedure and remained ventilator dependent. The cause of death was recurrent pulmonary sepsis with pulmonary failure. No episodes of bleeding ensued after the last surgery.

Discussion

The clinical and pathologic features of the solitary rectal ulcer syndrome were first observed by Curveillier in 1830 and were first described in detail by Madigan and Morson (2). The most common features of this entity are passage of small amounts of blood and mucus per anus. Gross inspection of a typical ulcer reveals a leathery, light-colored lesion which is depressed from the surrounding mucosa. The lesion has a mean diameter of 2–4 cm and is usually 7–10 cm from the anal verge. Further investigation of this condition has shown that not all lesions are solitary, nor are they all ulcerated (1). No specific cause has been discovered, but theories of rectal prolapse, self-induced trauma, and pressure from extraluminal structures have all been advanced (1, 5, 7).

Although all ulcers bleed sparingly and intermittently, massive hemorrhage from this lesion is extremely rare. Treatment options for this life-threatening complication range from supportive care to abdominoperineal proctectomy. A brief summary of all previously reported cases of massive hemorrhage from solitary rectal ulcers is presented in the Table. Dalancy and Hitch used local suture ligation and diverting colostomy to ultimately control a bleeding ulcer in three patients (4). The only other case report that specifically describes emergent laparotomy involves an ulcer in the proximal rectum thought to be caused by pressure from a uterine fibromyoma (7). After total hysterectomy, a colostomy was created and all bleeding ceased. In the series of Madigan and Morson, one patient came to major surgery to arrest bleeding, which recurred intermittently for one month. A complete rectal excision was curative after a diverting colostomy alone proved inadequate.

Success with local suture ligation is described by Duff and Wright in six patients with massively bleeding ulcers who were not candidates for major surgery (8). All the patients were severely debilitated from sepsis and multisystem disease. Although ligation controlled the acute bleeding, no follow-up is presented. The patients described in this case report underwent two laparotomies for the same massively bleeding rectal ulcer. Given the success of Dalancy and Hitch, definitive control with a local procedure and diversion was anticipated. Electrofulguration was elected in case 1 because of the size of the ulcer; suture ligation of bleeding sites was technically possible in case 2. Both local procedures failed. Interestingly, local treatment with proximal diversion has been notoriously unsuccessful in

TABLE

Summary of Previously Reported Cases of Massive Hemorrhage Secondary to Benign Solitary Rectal Ulcers

Ref. (no.)	Demographic data	Procedure	Outcome
Madigan (2)		Rectosigmoid resection and primary anastomosis	Recurred 16 yr later at site of anastomosis
		Rectosigmoid resection and primary anastomosis	Recurred 7 mo later but healed after 2 yr
		Proximal colostomy	Recurred after 4 mo. Required colon resection
	Pt also had prolapse	Transverse colostomy	Bleeding recurred. Required colon resection
	Pt also had prolapse	Local rectal amputation and colostomy	Chronic bleeding, eventually stopped
	Pt also had ca at 14 cm	Anterior resection of carcinoma (not ulcer)	Ulcer healed
Dalancy (4)	54 yo female, cerebellar fossa meningioma	Local electrical cautery	Rebled day 2. Colostomy and oversewing performed later
	47 yo female, severe diabetic ketoacidosis	Suture ligation	No rebleeding. Died after 1 wk due to ketoacidosis
	57 yo male, cardiac arrest	Suture ligation and diverting colostomy	No rebleeding
Haycock (7)	42 yo female, uterine fibroids	Hysterectomy, double-barrel colostomy	No rebleeding
Duff (8)	liver failure and/or CNS disease	Suture ligation	No rebleeding
	liver failure and/or CNS disease	Suture ligation	No rebleeding
	liver failure and/or CNS disease	Suture ligation	No rebleeding
	liver failure and/or CNS disease	Suture ligation	No rebleeding
	liver failure and/or CNS disease	Suture ligation	No rebleeding
	liver failure and/or CNS disease	Suture ligation	No rebleeding
	liver failure and/or CNS disease	Rectal packing	No rebleeding
		Resection including ulcer and Hartman	No rebleeding
		Resection including ulcer and Hartman	No rebleeding

healing rectal ulcers operated on for non-life-threatening conditions (1, 2). This observation, combined with the poor wound healing in chronic renal failure, most probably caused case 1 to rebleed once the eschar on the ulcer had sloughed. In both cases, a decision was reached to perform a definitive removal of the ulcer.

For less severe cases of rectal bleeding secondary to solitary rectal ulcers, new, noninvasive treatment modalities are available. In a recent report, Rau et al. (9) used the Nd:YAG laser to treat 14 patients who had histologically proven benign solitary rectal ulcers. Thirteen of the 14 patients were asymptomatic following a mean of 2.3 treatments.

Anterior rectosigmoid resection allows for removal of all the rectum to the dentate line via an abdominal approach. Despite the presence of systemic medical disease, as in the patients described, extensive surgery may be necessary to remove the ulcer and prevent exsanguination. In patients who have systemic medical disease, Goligher recommends abdominoperineal resection as the procedure of choice (1). This, however,

requires a perineal dissection, which adds to the morbidity of the abdominal procedure. Avoiding such a dissection in patients who have coagulopathies, multiple medical problems, and immunosuppression is probably beneficial. We, therefore, strongly recommend an abdominal approach only for massively bleeding rectal ulcers. This should allow for removal of the rectal segment containing the rectal ulcer in all patients.

In summary, patients with a massively bleeding rectal ulcer that does not stabilize with supportive therapy must be considered for resective surgery. The use of suture ligation and fulguration alone appears to work at least as a temporary measure in patients unable to tolerate a more extensive procedure. Local ligation with or without diversion has occasionally been successful in controlling bleeding, even though nonbleeding rectal ulcers have not been shown to heal using this modality. Should bleeding continue or recur, the surgeon must be prepared to excise that portion of the rectum containing the ulcer. We feel that this is best accomplished with abdominal rectosigmoidectomy.

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Pharmacokinetic Considerations in Phenytoin Pharmacotherapy:

Preventing Overdoses and Underdoses

LISA M. PROFETA, PHARM.D., KEITH BRADBURY, M.S., RPH, B.C.P.S., AND BERNARD MEHL, D.P.S.

ANTICONVULSANT AGENTS such as phenytoin have the ability to depress aberrant neuronal discharges in the central nervous system, thus preventing or terminating seizure activity. Phenytoin (Dilantin) is a hydantoin anticonvulsant that inhibits pharmacologic seizure activity at the motor cortex. Unlike the many agents that have first-order pharmacokinetics, phenytoin is metabolized in a capacity-limited fashion (Michaelis-Menten pharmacokinetics). Consequently, when phenytoin doses are increased, plasma concentrations rise disproportionately. Therefore, monitoring of serum drug concentration is imperative with any change in dosage. In phenytoin therapy, patients with hypoalbuminemia or renal failure and patients receiving phenytoin suspension plus concomitant enteral tube feedings encounter frequent problems. Management of these groups of patients is addressed here to help prevent overdosing or underdosing of phenytoin.

Phenytoin is 90% bound to plasma proteins, mainly albumin. Phenytoin's effectiveness in preventing seizures is closely correlated with serum concentration. Although the therapeutic range for phenytoin is generally considered to be 10 to 20 mcg/mL, this plasma concentration represents both protein-bound and protein-unbound phenytoin (1). The unbound or "free" phenytoin plasma concentration (usually 10% of total phenytoin level, that is, therapeutic range 1–2 mcg/mL) rep-

resents drug available to exert therapeutic or toxic actions. Changes in the extent of plasma protein binding affect the amount of "free" phenytoin and may alter serum level response relationships. "Free" phenytoin levels in excess of 2 mcg/mL are associated with drug toxicity or increased incidence of seizures. If possible, "free" phenytoin should be sampled for optimal dosing and efficacy.

Disease states or conditions in which plasma protein binding is decreased, including malnutrition, burns, trauma, neonates, nephrotic syndrome, cystic fibrosis, epilepsy, and uremia, alter the affinity of albumin for phenytoin, leading to an increase in the "free" unbound fraction. The same change takes place in patients taking drugs that compete for plasma protein binding, such as phenylbutazone, valproic acid, salicylic acid, and sulfisoxazole. One must closely monitor the patient's clinical status and response and adjust phenytoin levels accordingly, in addition to monitoring the therapeutic range of phenytoin.

Two formulas can be used clinically to adjust measured serum phenytoin concentrations in patients with hypoalbuminemia or acute or chronic renal failure (creatinine clearance <10 mL/min).

Hypoalbuminemia

$$\text{Concentration}_{\text{adjusted}} = \frac{\text{Concentration}_{\text{observed}}}{(0.2 \times \text{Albumin}) + 0.1}$$

Renal failure

$$\text{Concentration}_{\text{adjusted}} = \frac{\text{Concentration}_{\text{observed}}}{(0.1 \times \text{Albumin}) + 0.1}$$

Although these formulas are estimates, they are

From the Department of Pharmacy, The Mount Sinai Medical Center, New York, NY 10029. Address reprint requests and correspondence to Lisa Profeta, Pharm.D., Drug Use Evaluation Coordinator, Department of Pharmacy, Box 1211, One Gustave L. Levy Place, New York, NY 10029-6574.

helpful in empirically judging adjusted phenytoin concentration in patients who have hypoalbuminemia or renal failure. Patients may have total phenytoin levels within the therapeutic range when the actual level of free phenytoin is in the toxic range because of changes in plasma protein binding associated with either of these conditions.

Tables 1 and 2 may also be used as a quick and simple guide to determining the adjusted total phenytoin plasma concentrations or the desired therapeutic range in patients with hypoalbuminemia or renal failure (2, 3).

Dosing Guideline. When therapy with phenytoin is indicated, a loading dose should generally be administered. Since the volume of distribution of phenytoin is between 0.6 and 0.7 L/kg, each mg/kg administered intravenously will increase serum levels by approximately 1.5 mcg/mL. Therefore, a total intravenous loading dose of 15–20 mg/kg administered no faster than 50 mg/min is considered appropriate. If desired, this loading dose may be divided into several smaller doses administered over a period of several hours. If a subsequent loading dose is needed and a current serum level is available, the reloading dose can be calculated using the following formula:

$$\text{Loading Dose (mg/kg)} = 0.7 \text{ L/kg} \times (\text{desired level} - \text{observed level})$$

In adults, maintenance dosing is generally started at 5 mg/kg per day. In those patients whose levels are approaching the therapeutic range, dosage adjustments should be made in small increments of 100 mg or less because elimination of the drug is subject to saturable hepatic enzyme elimination pathways. Since the drug's pharmacokinetics can be nonlinear even at levels below the therapeutic range, steady-state levels may take as long as two to four weeks to achieve. Thus, dosage adjustments should not be made more frequently than every five to seven days.

Hypoalbuminemic patients receiving phenytoin should be carefully monitored for signs of toxicity even when reported levels are in the so-called therapeutic range. Evaluation of the patient's serum albumin and renal status should be made prior to dosage adjustments.

A problem may be encountered in patients receiving phenytoin suspension and concomitant enteral feeds via the nasogastric, jejunostomy, or gastrostomy tube. It has been suggested that these feedings may interfere with phenytoin suspension absorption; several studies have reported

TABLE 1
Patients with Low Serum Albumin

Measured total phenytoin concentration (mcg/mL)	Patient's serum albumin (gm/dL)			
	3.5	3.0	2.5	2.0
	Adjusted total phenytoin concentration (mcg/mL)			
5	6	7	8	10
10	13	14	17	20
15	19	21	25	30

TABLE 2
Patients with Renal Failure (CrCl ≤10 mL/min)

Measured total phenytoin concentration (mcg/mL)	Patient's serum albumin (gm/dL)				
	4.0	3.5	3.0	2.5	2.0
	Adjusted total phenytoin concentration (mcg/mL)				
5	10	11	13	14	17
10	20	22	25	29	33
15	30	33	38	43	50

subtherapeutic serum phenytoin levels in patients receiving concomitant enteral feeds and therapeutic doses of phenytoin suspension (4–7). One study dealing with this subtherapeutic problem questioned the actual potency of the phenytoin suspension, but in repeated analysis of the drug, each sample met required labeled concentrations (5). This interaction has been further documented in patients who required high phenytoin doses in order to maintain therapeutic serum concentrations and who experienced clinical signs and symptoms of phenytoin toxicity on discontinuation of enteral feeds. This interaction has been shown to occur both in patients receiving continuous enteral feeds and concomitant phenytoin suspension and in patients already stabilized on phenytoin suspension who required enteral feeds. To avoid this interaction, it has been recommended that continuous enteral feeds be held for two hours prior to and following phenytoin suspension administration, and that the tube be flushed with 60 mL of water after phenytoin administration. This interaction has also been documented in patients receiving crushed phenytoin tablets (Dilantin Infatabs) mixed with vanilla pudding containing similar enteral feed ingredients, such as corn oil, starch, caseinates, coconut oil, and carrageenan (8). In contrast to vanilla pudding, applesauce has been reported not to interfere with the absorption of other slow-release products and did not produce subtherapeutic serum phenytoin levels when given in combination (8).

In sum, patients receiving phenytoin who are

hypoalbuminemic or uremic or are receiving concomitant enteral tube feeding may require special consideration and monitoring to achieve appropriate drug therapy and optimal patient care.

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White Fibrous Papulosis



White fibrous papulosis is a benign disorder that most commonly occurs on the neck of elderly white women. It is characterized by indurated white papules, shown here on the posterior neck of a patient. The asymptomatic lesions can resemble those of pseudoxanthoma elasticum but are not associated with any systemic manifestations.—*Allen Sapadin, M.D., and Mark Lebwohl, M.D., Department of Dermatology, The Mount Sinai Hospital*

Prostate Cancer Screening Practices: Differences Between Clinic and Private Patients

NORVIN PEREZ, B.S., AND HARRY H. TSOU, B.S.

Abstract

How often prostate cancer screening tests are conducted in general practice is unknown. It is known that at the primary care level, health care delivered to uninsured and Medicaid patients and to privately insured patients differs. We investigated the frequency of digital rectal examination and prostate-specific antigen testing in a clinic (an internal medicine clinic) and a faculty private practice population at The Mount Sinai Hospital over a period of one year. A total of 165 male patients over 40 years of age were asked to respond to a survey questionnaire; 142 interviews were completed (62 private and 80 clinic). Chart and computer database review were used to record the last serum prostate-specific antigen test performed. There was no difference in age distribution between the two groups. The private practice patients were more likely to be insured and college educated, whereas the clinic patients were more likely to have no more than an eighth-grade education and to receive Medicaid. The two groups did not differ in frequency of digital examination within the past year. Private patients were six times more likely than clinic patients to have had prostate-specific antigen screening and seven times more likely to receive both of the recommended prostate screening tests within the past year. Results also showed that 25% of all patients were not screened for cancer by digital rectal examination. Study of a larger population is recommended to further corroborate these findings.

PROSTATE CANCER was the most commonly diagnosed cancer in men in the United States in 1993; it was also the second leading cause of cancer-related mortality in men. In the United States 200,000 new cases of prostate cancer were expected to be diagnosed in 1994 (32% of all cancer in men). Furthermore, it is second only to lung cancer as the leading cause of cancer-related death, causing 38,000 deaths per year. In the past decade, the number of prostate cancer cases has increased steadily by 8%–10% annually (1). Thirty to forty percent of men with newly diagnosed prostate cancer cannot be cured (2). Thus confronting this health crisis is urgent. To detect

prostate cancer at its earliest stages, screening practices must be implemented. In the absence of definitive data to justify the use of multiple screening tests for lowering the mortality of prostate cancer (3–6), both the American Cancer Society (ACS) and the National Cancer Institute (NCI) have recommended an annual digital rectal examination (DRE) and a prostate-specific antigen blood test (PSA) for screening of prostate cancer beginning at 40 years of age (2).

Many articles in the medical literature have reviewed the accuracy of prostate cancer screening tests. The majority of these investigations have been conducted in urology clinics and private urology practices. In these specialized practices, every man over the age of forty had received appropriate prostate cancer screening tests. Therefore, these studies do not represent the actual implementation of prostate cancer screening tests in general practice settings. We feel it is important to investigate the frequency with which males over forty are being screened for

The authors, fourth-year medical students at the Mount Sinai School of Medicine, completed this study for their Community Medicine rotation.

Address reprint requests to Norvin Perez, 108 East 96th Street, Apt. 15A, New York, NY 10128.

prostate cancer when they visit their general practitioners.

Many studies have reported disparities in cancer screening practices for populations of low and high socioeconomic status. In a breast cancer study, it was observed that uninsured and Medicaid patients were less likely to receive an annual mammogram than their privately insured counterparts (7–9). Afro-Americans not only make up a significant portion of the lower socioeconomic class in the United States, they are also at increased risk for developing prostate cancer. We believe it is imperative to investigate whether prostate cancer screening practices are being implemented equally for both insured and uninsured populations.

Methods

Setting and Study Population. The purpose of this study was to compare prostate cancer screening practices between private (insured) and clinic (uninsured) settings. Two sites were chosen for this study: Internal Medicine Associates (IMA) and Faculty Practice Associates (FPA). IMA represents a patient population of lower socioeconomic status, where most patients receive Medicaid or Medicare with Medicaid. FPA is a private general practice office where most patients are privately insured or have privately supplemented Medicare. Physicians in FPA are attendings in the Department of Medicine at the Mount Sinai Medical Center in New York City. Physicians in the IMA are mostly residents working under the supervision of an attending and a chief resident. Both facilities are affiliated with the medical center. Physicians on staff alternate between the two locations. Both settings are general internal medicine practices.

Because of the recommendations for prostate cancer screening by the American Cancer Society and the National Cancer Institute, all patients older than forty were invited to participate in the study. After an interview and questionnaire were completed, chart and computer database review were used to supplement laboratory data.

Survey Instrument. The study instrument was a written survey questionnaire, and the study design was cross-sectional. The questionnaire was administered by an investigator who recorded patients' responses. A bilingual investigator administered the questionnaire to Spanish-speaking patients. The survey consisted of 18 questions, developed by the authors. The subject had to answer 17 of these; the last question was filled out by the interviewer after completing a

chart and computer database search for the last PSA test administered to that patient. Patients were first asked if they had ever been screened for PSA; a chart and computer database were then reviewed to confirm patient responses.

Survey technique was chosen for two reasons. First, all yearly digital rectal examinations given during an annual physical examination could not be expected to be performed at the study site, making chart review alone an inadequate source for this information. Second, since some sociodemographic information, such as the patient's knowledge and awareness of prostate cancer and his level of education, were also a concern in this study, a retrospective chart review would have been inadequate. Participation in this study was strictly voluntary.

The purpose of the patient's visit was categorized as either "genitourinary" or "non-genitourinary." Genitourinary symptoms were defined as micturition-related problems. Seventy percent of patients with prostatic cancer experience some difficulty with micturition (10). This categorization attempted to identify any potential biases by the general internist during the physical examination if the patient had symptoms related to prostate cancer or benign prostate hyperplasia. For all survey questions, an additional response of "I do not know" was included to reduce the amount of guessing. A blank space was provided for questions with nondefinitive answers.

The questionnaire addressed 5 major issues:

- Patient's sociodemographic status. This included all major socioeconomic characteristics that could be recorded without any bias from the investigators and mathematical analysis. Health plan, education, ethnicity, and marital status were included for comparison between groups. Health plans were categorized as Medicaid, private insurance (private primary insurance or Medicare with private supplemental insurance) and Medicare with Medicaid. All Hispanics were classed as "Hispanic," whether they were white, black, or of mixed race.
- Patient's health habits. It is believed that there are some environmental contributions to the etiology of prostate cancer. Therefore, information on tobacco and alcohol use was obtained.
- Patient's knowledge of the anatomic location of the prostate. We assumed that patients who were not aware of the prostate's anatomic location were less likely to be aware of the potential risks of prostate cancer. Also, Brown et al. (7) found that patients' level of education and knowledge of early warning signs of cancer

were associated with the use of cancer screening tests.

- Patient's personal and family history of cancer, because there is a positive relationship between the number of blood relatives with prostate cancer and the risk of developing this disease.
- DRE and PSA received by the patient during the past year.

In statistical analysis, differences in the practice of prostate cancer screening in the two practices were evaluated by chi square test. Continuous variables (such as age) were analyzed by Student's *t*-test.

Results

Demographic Information. *Questionnaires completed:* During a two-week period, 165 patients older than 40 visited the clinic and private office. All of them were asked to participate. Thirteen patients refused to complete the questionnaire (8 from the IMA and 5 from the faculty practice); 3 patients were unable to complete the questionnaire due to old age; and 7 men were under the age of 40. A total of 142 questionnaires were completed. Of these usable questionnaires, 80 (56%) were from the clinic and 62 (44%) from the private practice. Of the 142 surveys returned, 97 were in English and 45 (all from the clinic) were in Spanish.

Age: Respondents had an overall mean age of 63 years (SD $\pm$ 12.4, median 64 years), with a range of 40 to 96 years. The mean age and standard deviation of the clinic group was 62 $\pm$ 11.5 years, and the private practice group 65 $\pm$ 13.4. There were no significant differences.

Health insurance: There were significant differences in health insurance coverage by chi-square test, $p < .0001$. All Medicaid patients visited the clinic. The clinic patients were 3.8 times more likely to have Medicare with Medicaid than private patients. Ninety-nine percent of patients with private insurance visited the private practice office (Table 1).

Race: All Hispanic patients were seen in the clinic practice. White patients were 8 times more likely to be seen in the private practice. Afro-Americans were 2.5 times more likely to be seen in the clinic. A significant difference in ethnicity existed between the clinic and private patients. The majority of private patients were white (87.1%); the majority of the clinic patients were Hispanic (56.3%) ($p < 0.00$, chi square) (Table 1).

Marital status: Although four categories of marital status were identified in the questionnaires, for the purpose of statistical analyses, the

investigators combined single, widowed, and divorced patients into a single "unmarried" category. Seventy-six patients (53.5%) were married and 66 patients (46.5%) were unmarried. There are significant differences in marital status between clinic and private practice patients (p 0.024). The clinic patients were 1.78 times more likely to be unmarried (single, widowed, or divorced) (Table 1).

Education: Levels of education attained by patients were translated into years for calculation. High school completion was considered to be 12 years of education; college degree, 16 years; master's degree, 18 years; Ph.D. degree, 21 years; MD degree, 20 years, and JD degree, 19 years. The mean educational level for clinic patients was 8.15 $\pm$ 4.12 years, and for private practice patients, 16.24 $\pm$ 3.55 years (p 0.000 by Student's *t*-test).

Health habits: There were significant differences in the number of patients who smoked more than a pack of cigarettes a day (p 0.001) and the number of patients who consumed more than three alcoholic drinks a day (p 0.027). In the clinic patient group, there were 15 smokers (18.8%); in the faculty practice, there was only 1 (1.6%) smoker. The clinic patients were 12 times more likely to smoke more than one pack a day than were private practice patients. Six patients (7.5%) in the clinic group admitted to drinking more

TABLE 1
Characteristics of Study Participants

	Total (%)	Clinic (%)	Private (%)	RR
Insurance status				
Medicaid	34 (23.9)	34 (42.5)	0 (0)	—
Medicare	47 (33.1)	39 (48.8)	8 (12.9)	3.78
Private*	52 (36.6)	1 (1.3)	51 (82.3)	0.02
Cash	4 (2.8)	3 (3.8)	1 (1.6)	2.38
Other	5 (3.5)	3 (3.8)	2 (3.6)	1.19
Ethnicity				
White	62 (43.7)	8 (10)	54 (87.1)	0.12
Afro-American	34 (23.9)	26 (32.5)	8 (12.9)	2.52
Hispanic	45 (31.7)	45 (56.3)	0 (0)	—
Other	1 (0.7)	1 (1.3)	0 (0)	—
Marital status				
Married	76 (53.5)	34 (42.5)	42 (67.7)	0.628
Unmarried†	66 (46.5)	46 (57.5)	20 (32.3)	1.780
Medical sophistication				
1. Do you have a prostate?				
Yes	110	55 (68.8)	55 (88.7)	0.77
No	14	9 (11.3)	5 (8.1)	1.39
I don't know	18	16 (20)	2 (3.2)	6.25
2. Prostate site				
Near stomach	1	0 (0)	1 (1.6)	0
Near lungs	3	3 (3.8)	0 (0)	—
Near bladder	103	49 (61.3)	54 (87.1)	0.70
I don't know	35	28 (35.0)	7 (11.3)	3.10

* Patients with private primary insurance or privately supplemented Medicare coverage.

† Single, widowed, or divorced.

than 3 alcoholic beverages a day, but none of the private patients reported that level of drinking. Finally, no patients in this study admitted to any illegal drug abuse.

Questions related to Prostate Cancer. Purpose of office visit: Patients were asked if the visit was related to micturition problems. Eight patients (10%) in the clinic and 4 patients (6.5%) in the private practice had urinary complaints during the time of visit. No significant difference was found. Purpose of office visit included annual physical examination, regular check-up, and health-related problems that could or could not include urinary complaints. Patients who visited the office for medication renewals were not interviewed because most came only to pick up a prescription and did not see the physician.

Knowledge of prostate and its location: There was a significant difference in awareness of prostate status (presence, absence or not knowing). Twenty percent (n 16) of clinic patients and only 3.2% (n 2) of private patients (p 0.007) did not know whether they still had their prostate. The clinic patients were six times less likely to know whether they had a prostate (Table 1).

Sixty-three percent of clinic patients (n 49) and 87.1% of private patients (n 54) were aware of the location of the prostate. The relative risk of clinic patients not knowing the location of the prostate was 3.10 and the statistical significance was p 0.002 (Table 1).

Personal and family history of prostate cancer and other cancers: Neither personal nor family history of prostate cancer was statistically different between clinic and private patients. Only personal history of cancer reached statistical significance by chi-square test (p 0.009). Five (6.3%) clinic patients and 13 (21.0%) private patients reported past cancer. However, 8 of 13 private patients who had cancer had cancer of the skin. If these cases are excluded, significance is lost.

Administration of DRE and PSA. DRE: Patients were asked when prior to the current visit they had last received a DRE. Of the entire population interviewed, 72% had received a DRE during the last year. Patients were also asked if they had undergone a DRE during their current visit.

The last time the entire population interviewed had a DRE had a mean of 15.8 months and a median of 8 months (SD 23.1). If a patient had received a DRE on the current visit or within twelve months, he was placed into one group; if the patient gave any other response, he was placed into a second group. Chi-square results showed that in both settings patients were

TABLE 2
Differences in Screening for Prostate Cancer between Private and Clinic Patients

	Private (%)	Clinic (%)	<i>p</i>	<i>RR</i>
PSA	42/62 (67.74)	8/80 (10)	0.0	6.69
DRE	45/62 (73)	57/80 (72)		
DRE + PSA	34/62 (54.84)	6/80 (7.5)		

equally likely to have received a DRE within the past year (73% private versus 72% clinic). The same question was analyzed by t test. No significant difference was found (Table 2).

PSA: Chart review and computer database search were used to determine if patients had received a PSA in the past. Of the entire population interviewed, 27% had a PSA ordered. The mean time since last PSA was 5.6 months, median 4 months (SD 7.6, range 48).

In the private setting, 42/62 patients had a PSA, whereas in the clinic setting 8/80 patients had that screening test.

The mean time interval from order for PSA to time of survey was 5.9 months for private patients and 4.2 months for clinic patients. There was no statistical difference by Student t test.

Both DRE and PSA within past year: Chi-square analysis was performed to determine how likely it was for a patient to receive both DRE and PSA. A patient in the private setting was seven times more likely to receive both screening tests during the last year than was a patient in the clinic setting (P 0.00).

Marital Status as a Confounding Variable. There was a significant difference in patients' marital status in the clinic and the private setting. We investigated a possible relationship between marital status and practices in screening for prostate cancer during the past year. We

TABLE 3
Marital Status and Prostate Cancer Screening in Private and Clinic Settings

Setting	Screened (%)	Not screened (%)	<i>p</i>	<i>RR</i>
Private				
married	39/42 (92.9)	3/42 (7.1%)		
single, widowed, divorced	15/20 (75)	5/20 (25)	0.05	1.24
Clinic				
married	28/34 (82.35)	6/34 (17.65%)		
single, widowed, divorced	33/46 (71.74)	13/46 (28.26)	0.27	1.1

found a trend in the private setting for more married than unmarried patients to undergo proper screening—being screened by both tests (P 0.05). Marital status did not affect screening in the clinic setting (Table 3).

Discussion

The null hypothesis for this study was, "There is no difference in prostate cancer screening (DRE and PSA) during the past 12 months received by a population that attends a private practice and that which attends a clinic." Because a significant difference was found, the null hypothesis was rejected. A type I error would have occurred if a large portion of clinic patients received PSA testing outside of the medical center. This study has no evidential resource that would permit dismissing the prior statement. Therefore, the possibility of a type I error cannot be discarded.

Approximately 45% of private patients were not undergoing screening according to the ACS recommendation (>40 years of age, DRE and PSA). Unfortunately, although we observed that 90% of clinic patients were not being properly screened, the actual rate of implementation could not be estimated accurately because some clinic patients did not attend the clinic consistently; therefore, the possibility of their receiving a PSA test from another source cannot be ruled out at this time.

Brown et al. (7) reported that 47.1% of their random general population underwent DRE as a screening test at one time or another. In their study, whites were 1.39 times more likely to have undergone DRE than Hispanics. In our investigation, 72% of the population had DRE during the year preceding the study. There were no racial differences in the frequency of annual DRE. Since Hispanics comprised a large proportion of the clinic population (56.3%) and whites the majority of the private practice population (87%), our data should closely resemble that in Brown et al. However, this is not the case. This new finding might suggest an increased implementation of DRE among primary care physicians and their greater acceptance of ACS recommendations in the years since 1990, when Brown et al. was published.

Clinic patients were less likely than private patients to know whether they had a prostate and where it was anatomically. Using level of education as an indicator of socioeconomic status, Brown et al. (7) reported a relative risk of 1.19 of knowledge of DRE between his study groups (whites versus Hispanics). Even though the His-

panic (clinic) population in our study received more DREs than did Brown's Hispanic population, Hispanics in our study did not know the purpose of this test. This can be reflected by a higher relative risk of lack of knowledge observed in our study (3.10, versus 1.19) in Brown et al. (7).

The American Urological Association (AUA) recommends the same screening tests for prostate cancer as the American Cancer Society (ACS) and the NCI, but recommends the starting age of 50 rather than 40. Older age in a population screened by DRE and PSA should increase the combined specificity of these two tests. Only 54% of the private patients in the study reported here underwent the recommended prostate cancer screening during the year prior to the study. One might question why the figure was not 100%. One explanation for lack of compliance with the recommendations of ACS and NCI might be that internists have been following the AUA recommendations. Fourteen percent of all patients in our study population were under the age of 50. Using the AUA starting age of 50 years, 28% of the private and 79% of the clinic population in the study reported here were not properly screened by both tests for prostate cancer within the last year.

The disparities we found in prostate cancer screening practices between the two populations cannot be solely explained by confusion between conflicting prostate cancer screening recommendations (ACS vs. AUA vs. NCI). If confusion were the cause, no difference in screening practices would have been found. There are four possible explanations for our findings. First, physicians in the clinic may be less informed than those in the private practice setting, perhaps because physicians in the clinic are still in training. Second, because of the low reimbursement fees of Medicare and Medicaid physicians in the clinic setting may have been educated not to order an additional PSA serum test, but this cannot be at issue because physicians in this study were not compensated by number of tests ordered. Third, patients who attend a private practice office are better informed and may, out of a sense of urgency, convey to their physicians their desire to have a PSA. Finally, physicians may have less of a sense of urgency about diagnosing prostate cancer in patients of lower socioeconomic status. A combination of these factors may also account for the study results.

Our results indicate that despite the proximity of the two practice settings, about 45% of the men who visit private general practice offices and at least 90% of the men who visit clinics had not received both tests within the year preceding the

study. This conclusion is in accord with other studies that have examined the quality of health care delivered to different social classes (7–9). Prostate cancer is a disease that has a long asymptomatic latent phase. That latency, combined with inadequate screening, particularly in men under 50, could result in higher morbidity and mortality from advanced stage of cancer at diagnosis. Today, 30%–40% of all diagnosed prostate cancer cannot be cured (2). Further studies in other practice settings must be done to evaluate the quality of health care delivered.

Conclusions

This survey shows differences in the practice of prostate cancer screening between the uninsured and the insured patient. Four conclusions can be drawn:

- There was no difference between the private and clinic populations in the frequency of DRE received within the year preceding the study (72% and 73% respectively).
- There was a significant difference in the frequency of PSA performed in the year preceding the study by practice setting. Only 10% of the clinic patients received the PSA test, whereas 68% of the private group did—an almost seven-fold difference.
- The frequency of performance of both DRE and PSA within the year prior to the study in the clinic and the private patients differed significantly. Only 7.5% of the clinic group received both the DRE and the PSA test within the year, as compared with 55% of private patients. Private patients were seven times more likely to receive both tests, as recommended by the ACS and the NCI.
- How closely the results of this investigation reflect the rate of implementation of prostate cancer screening in private primary care and in clinics needs further investigation.

Having a general practitioner as a personal physician is one of the most important factors allowing an individual to benefit from preventive medicine. General practitioners not only offer annual check-ups, they also provide immunizations, health education, personal consultations, and early detection of diseases such as prostate cancer. We observed a disparity in the prostate cancer screening practices between populations of

high and low socioeconomic status in general practice settings. This finding might in turn suggest the possibility of other inequalities in the practice of preventive medicine among general practitioners. If this is the case, we could conclude that the practice of preventive medicine should include not only the education of patients but also the education of physicians.

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Abstracts

These 15 abstracts, all by principal investigators in the Department of Medicine, Mount Sinai Services at the Queens Hospital Center (Jamaica, NY) of the Mount Sinai School of Medicine, New York, NY, were presented at the Queens Hospital Center Department of Medicine Research Day on April 12, 1995. Three of the abstracts have been published elsewhere; a citation of publication is supplied for each.—Fred Rosner, M.D., FACP, Director, Department of Medicine, Queens Hospital Center

Research in Medicine Queens Hospital Center

1. Fluvastatin (Lescol): Short-Term Efficacy and Safety. I. Sachmehchi, A. Kissin, M. Sharafatkah. Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

Background: Fluvastatin is a synthetic HMG-COA reductase inhibitor which decreases cholesterol synthesis. Fluvastatin is safe, effective, and well tolerated in long-term treatment of primary hypercholesterolemia.

Methods: We examined the efficacy and safety of 20 mg fluvastatin daily in reducing total cholesterol and low-density lipoprotein (LDL) in patients with hyperlipidemia secondary to noninsulin-dependent diabetes mellitus (NIDDM). Eight men and five women (age range 40–85 years) were studied. Lipid profiles, liver function, and creatine phosphokinase (CPK) levels were determined before and 8 weeks after initiation of fluvastatin.

Results: Of the 13 patients, only 9 completed the study. For these 9 patients, the range of baseline total cholesterol level (all results given in mg/dL) was 208–294 (mean 252.11 ± 8.84 SEM) and the range of LDL 139–204 (mean 168.78 ± 6.95 SEM). After 8 weeks of therapy, the 9 patients who completed the study had lower total and LDL cholesterol. Total cholesterol range was 183–265 (mean 208.33 ± 9.43 SEM), with a mean reduction of 17.3%. LDL cholesterol range was 76–188 (mean 129 ± 8.55 SEM), with a mean reduction of 23.57% ($P \leq .001$ pre vs post treatment by paired *t*-test for both total and LDL cholesterol). Of the four patients who discontinued the treatment because of its adverse effects, two had elevated levels of CPK with muscle pain and two had muscle and joint pain but normal levels of CPK. One of the 9 patients had transient gastrointestinal discomfort but continued taking the medication.

Conclusions: Short-term fluvastatin therapy is effective in reducing total cholesterol and LDL in patients with hyperlipidemia caused by NIDDM. However, serious short-term side effects may occur in a significant number of patients.

2. Unplanned Extubations in an Inner-City Hospital Medical Intensive Care Unit. M. Sokhandan, S. Abraham, I. Westbrooke, R. Parris, J. Fleischman. Pulmonary and Critical Care Medicine, Nursing Department and Respiratory Care Department, Queens Hospital Center.

Background: Approximately 15 million patients undergo endotracheal intubation annually in the United States. Unplanned extubations (UE) are reported to occur in 8%–16% of all intubated patients in community hospital intensive care units (1–3), and the reintubation rate is approximately 50% (4, 5). Previous studies have examined the rate of

UE, but little attention has been paid to the various factors involved in these events. UE may be due to accidental removal of the endotracheal tube (ETT) during routine nursing care or to patient movements, or it may be the result of intentional self-extubation.

We conducted a study of all intubated patients in an adult medical intensive care unit in an inner-city hospital to determine the rate of UE in our patient population.

Methods: The rate of unplanned extubations was determined for all intubated patients during two time periods: Period A (1/94–6/94), when only conventional monitoring—securing ETT as needed—was performed, and Period B (7/94–12/94), when close monitoring was performed.

Close monitoring included serial measurements at the patient's bedside of manner of securing ETT, location of ETT by x-ray or lipline, degree of sedation or agitation, and quantity of tracheal secretions. Other than these differences in monitoring, there was no difference in patient management in the two periods.

Unplanned extubations were classed as either accidental extubations or self-extubations. The rate of reintubation was calculated for periods A and B.

Results: During the study period (January–December 1994), a total of 205 patients were intubated in the Medical Intensive Care Unit, and the overall unplanned extubation rate was 17%, compatible with national averages (1). The rate of reintubation in both study periods was approximately 45%, compatible with national averages (4, 5). Both the number of patients experiencing UE and the number of UE fell significantly from Period A to Period B.

Period	Total no. of intubated pts	No. of pts with UE (%)	Total no. UE (%)
A	98	22 (22%)	30 (30%)
B	107	13 (12%)	17 (16%)
P		0.0132	0.0196

Clinical features of patients experiencing UE were similar in both periods. Mean age was 48 years in Period A and 51 years in Period B. Female-to-male relationship was 12:10 in Period A and 8:5 in Period B. Underlying medical illnesses included pulmonary disease, 9/22 (40%) in Period A and 4/13 (30%) in Period B; CHF, 3/22 (13%) in Period A and 2/13 (15%) in Period B; miscellaneous diagnoses, 10/22 (45%) in Period A and 7/13 (53%) in Period B. However, in Period B the percentage of substance abusers among patients experiencing UE was greater than in Period A.

The percentage of accidental extubations was similar in both study periods: Period A, 5/98 (5%); Period B, 5/107 (4.6%). However, the percentage of self-extubations fell significantly from Period A (13/98, or 13%) to Period B (2/107, or 1.8%). The number of UE due to unclear causes was 4/98 (4%) in Period A and 6/107 (5.6%) in Period B.

Despite the much larger percentage of substance abusers among patients in Period B, the percentage of UE decreased significantly. Decreased agitation in Period B correlated with the reduction in the

percentage of UE that occurred during this period.

	Period	
	A	B
	No. (%)	No. (%)
Substance abuse	6/22 (27%)	6/13 (46%)
Agitation	8/22 (36%)	2/13 (15%)
Pts with UE	22/98 (22%)	13/107 (12%)

Conclusions: During the period of close monitoring and observation, the number of patients experiencing UE and the total number of these events decreased significantly. Decreased agitation during Period B correlated with the reduction in the number of UE.

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3. Assessment of Asymptomatic Ischemia in Subjects with Spinal Cord Injury (SCI). M. Raza, W. A. Bauman, Ziev Chayes. Mount Sinai Services at Queens Hospital Center (MR) and Bronx Veterans Affairs Medical Center.

Background: More than 250,000 subjects with spinal cord injury exist in the U.S. With the improvement in general primary care and use of antibiotics, the prognosis of SCI patients has improved. Cardiovascular disease has emerged as the major cause of death among SCI subjects. Such patients have multiple risk factors for coronary artery disease (CAD), but despite significant degree of disease, they may be asymptomatic. There is little information on the assessment of CAD in subjects with SCI.

Methods: Twenty male veterans attending the outpatient department at V.A. Medical Center in the Bronx, meeting the inclusion criteria of the study, are the subject of this report. All the participants in the study were asymptomatic with normal resting ECG. Arm exercise ergometry with ECG monitoring and thallium myocardial perfusion scintigraphy were performed. Those with abnormal scintigram results had 24-hour Holter monitoring with a 3-channel Marquette recorder and analyzer for the detection of arrhythmias and ischemia. All 3 channels were used for ST segment analysis; the evaluation for ischemia was 1 mm or more ST depression 80 msec beyond the J point for more than one minute.

Results: On arm exercise ergometry, only 5 of 20 (25%) patients had evidence of asymptomatic ischemia, whereas 13 subjects (65%) had scintigrams consistent with ischemia, ischemia with scar, or scar only. Eight (60%) of the thirteen subjects with abnormal scintigrams would have been missed on arm exercise ergometry alone. None of the subjects with abnormal scintigram had significant arrhythmia or episodes of silent ischemia on Holter monitoring.

Conclusions: Although the numbers are small, the study indicates that Holter monitoring is not useful in the assessment of ischemia in SCI patients. Arm exercise ergometry has low sensitivity in the detection of ischemia in patients with SCI. A stress thallium myocardial perfusion study is the most sensitive test in detection of ischemia in subjects with SCI. Assessment of silent ischemia and its appropriate management is indicated in SCI patients undergoing surgery, exercise training, rehabilitation, and so on, since silent ischemia may be an adverse prognostic indicator (1, 2).

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4. 25-Hydroxyvitamin D in Elderly Nursing Home and Enriched-Housing Residents in New York City. C. Feiner, M. Mulvihill, B. Taylor, W. Bauman, H. Smith, E. Weintraub, P. Tsitouras. Mount Sinai Services at Queens Hospital Center, Jamaica, New York; Jewish Home and Hospital for Aged, Bronx, New York; and Bronx VA Medical Center, Bronx, New York.

Published in *J Am Geriatr Soc* 1993; 41:SA-38.

5. Jaccoud's Arthropathy Associated with Inflammatory Bowel Disease: Case Report. A. Opran, A. Haque, E. Lipstein-Kresch, J. Goyzueta. Mount Sinai Services at Queens Hospital Center.

Background: Jaccoud's arthropathy (JA) is a nonerosive deforming arthritis first noted in association with rheumatic fever but later described in association with systemic lupus erythematosus, scleroderma, hypogammaglobulinemia, Ehlers-Danlos syndrome, and neoplastic diseases. Clinically JA is a deforming arthritis involving mostly the peripheral joints, particularly the hands, with ulnar deviation and flexion deformities evident at the metacarpophalangeal joints, sometimes combined with hyperextension at interphalangeal joints. Characteristic radiographs show the lack of osseous erosions and joint deformities, differentiating JA from rheumatoid arthritis (RA) and other inflammatory synovial processes.

The peripheral arthropathy associated with inflammatory bowel disease (IBD) is commonly asymmetric and starts as acute synovitis that usually resolves within six to twelve weeks. Large joints of the lower extremities are usually more affected, with predilection for the knees, hips, and ankles, in that order.

Case Report: Our patient, a 41-year-old Guyanese woman, has longstanding, biopsy-confirmed IBD with multiple exacerbations and associated peripheral arthropathy. She has no axial articular involvement and has normal radiographs of the LS spine and SI joints. The articular manifestations are exclusively peripheral and started soon after the IBD was diagnosed. The patient's IBD-associated arthropathy exclusively involves the small joints of the hands and feet, clinically resembling RA. Although the patient was told that she had rheumatoid arthritis, her rheumatoid factor was negative and her x-rays do not show classic joint space narrowing and osseous erosions. The severity of the joint subluxations and deformity of the hands and feet with preserved joint space and minimal osseous erosions favor Jaccoud's-type arthropathy as the diagnosis.

Conclusion: We conclude that our patient has an unusual form of IBD-associated arthropathy resembling Jaccoud's arthropathy.

6. Gouty Sacroiliitis in the Absence of Tophi: Case Report. Nestor Nazareno, Mitchel Laks, Esther Lipstein-Kresch, Juan D. Goyzueta. Departments of Medicine and Radiology, Queens Hospital Center and Mount Sinai School of Medicine.

Background: Both acute and tophaceous gout primarily affect the appendicular skeleton and rarely affect the sacroiliac joints. Most patients in reported cases of sacroiliac gout share a common clinical profile. Almost all patients have long-standing gout, as evidenced by the presence of tophi on several articular and periarticular sites (suggesting that the disease process has been present for at least 10 years), or onset of gout at an early age (before age 20). Alarcon-Segovia (1) and Resnick (2) reported on patients with roentgenographic evidence of sacroiliac gout who had tophi and an early onset of gout.

Case Report: We report a case of gouty sacroiliitis in a patient with neither early onset of gout nor evidence of tophaceous gout.

Conclusions: We suggest that gout be included in the differential diagnosis of sacroiliitis even when onset is later in life or when tophi have yet to develop. Further studies are recommended to establish the true incidence of sacroiliac gout.

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7. Absence of Hydronephrosis in Cystinuria-Induced Sludge Obstructive Uropathy: Case Report. Victor Souza, Robert H. Smith, Juan D. Goyzueta. Departments of Medicine and Radiology, Queens Hospital Center and Mount Sinai School of Medicine.

Background: Cystinuria is an autosomal recessive disorder characterized by a defect in the transport of cystine and other dibasic amino acids (ornithine, lysine, arginine) in the epithelial cells of the renal tubule. Inadequate reabsorption of filtered and secreted cystine in the proximal tubule results in excessive amounts of cystine in the urine and in stone formation. This accounts for approximately 1% of all renal stones.

Sludge causing obstructive uropathy has been described (Nicholson R, Hewitt I, Kam A, Ureteric sludge syndrome, *Arch Dis Child* 1991; 66:344-346). The reported cases of sludge were due to uric acid, calcium oxalate, and cystine. The case of acute renal failure due to cystinuria-induced sludge had dilatation of ureters or hydronephrosis on ultrasonography.

Case Report: We describe a case of cystinuria-induced obstructive uropathy without the typical sonographic findings suggestive of obstruction. The patient's entire collecting system on the left side was filled with sludge, a fact not immediately appreciated on the sonogram. No acoustic shadowing suggestive of nephrolithiasis was demonstrated, and hydronephrosis was not evident.

Conclusions: Urinary tract obstruction without hydronephrosis has been reported in three settings: (a) early obstruction or acute complete obstruction when the collecting system is less responsive and has not had time to dilate; (b) mild obstruction; and (c) when the collecting system is encased by retroperitoneal fibrosis or tumor. We suggest the presence of sludge be considered when obstruction of the urinary tract is a strong possibility despite the absence of hydronephrosis.

8. Pseudomembranous Colitis without Diarrhea: Case Report. Daniel A. Blaustein, Charles R. Berman. Mount Sinai Services at Queens Hospital Center and Mount Sinai School of Medicine.

Background: Pseudomembranous colitis (PMC) is an infectious disease which typically produces profuse, watery, green, foul-smelling, or bloody diarrhea and cramping abdominal pain. High fever, leukocytosis, hypovolemia, dehydration, and marked abdominal tenderness are common in patients with PMC. Colitis without diarrhea is an extremely rare manifestation of this disease.

Case Report: A 72-year-old Haitian woman developed clindamycin-induced PMC. Despite a full course of metronidazole therapy, she remained febrile for 3 weeks. One of the studies undertaken to identify the cause of the fever was an abdominal/pelvic CT scan, which showed a diffusely edematous colonic wall with pericolonic inflammation and stool accumulation throughout the entire colon. These findings led us to perform flexible sigmoidoscopy that demonstrated classic pseudomembranes. The patient was treated with enteric vancomycin and promptly defervesced.

Conclusion: PMC should be considered in the differential diagnosis of fever of unknown origin, even in patients who do not have diarrhea.

9. *Mycobacterium avium intracellulare* Splenic Abscess: Case Report. Barbara T. Edwards, Ramit Kahlon, Juan D. Goyzueta. Department of Medicine, Queens Hospital Center and Mount Sinai School of Medicine.

Background: *Mycobacterium avium intracellulare* causes disseminated infection in patients with AIDS. The organism is an uncommon cause of splenic abscess.

Case Report: We describe a 47-year-old male intravenous drug user with AIDS who was admitted with fever and acute abdominal pain of the left side two weeks after completing a course of antibiotic treatment for *Staphylococcus aureus* endocarditis.

An abdominal ultrasound showed hepatosplenomegaly and a 4-cm irregular echogenic area in the spleen suggestive of a hematoma or an abscess. On noncontrast computed tomography scan, the spleen was seen to have multiple areas of low density in the periphery, representing splenic infarcts or possible abscess. The patient underwent splenectomy. Operative specimens showed numerous acid-fast bacilli subsequently identified as *M. avium intracellulare* by culture. The patient responded to isoniazid, rifampin, ethambutol, and pyrazinamide and was subsequently lost to follow-up.

Conclusion: This case illustrates an unusual presentation of a disseminated mycobacterial infection in a patient with advanced HIV disease.

10. The Pharmacokinetics of Acetazolamide during Chronic Ambulatory Peritoneal Dialysis. Michael H. Schwenk, Daniel A. Blaustein, John D. Wagner. Long Island Jewish Medical Center, New Hyde Park, NY; Mount Sinai Services at Queens Hospital Center.

Published in *Adv Perit Dial Int* 1994; 10:44-46.

11. Malignant Glucagonoma: Light Electron Microscopic and Immunohistochemical Study—Case Report. I. Sachmechi, S. Peykar, S. H. Shapiro. Departments of Medicine and Laboratories, Mount Sinai Services at Queens Hospital Center.

Background: Glucagonomas, tumors of α cells of human pancreatic islets, are often malignant. Malignant glucagonoma cells usually contain atypical granules (Drucker DJ, Asa SL, Silverberg J, Brubaker PL, Molecular and cellular analysis of a neoplastic A-cell tumor, *Cancer* 1990; 15:1762-1770).

Case Report: We report a case of malignant glucagonoma with typical α cell granules. A 43-year-old man had a pancreatic mass determined to be a malignant glucagonoma by light microscopic, immunohistochemical, and electron microscopic studies.

Microscopically, the argyrophilic and phosphotungstic acid hematoxylin (PTAH) positive tumor had glandular, ribbon like, and solid areas, and consisted predominantly of uniform cells. Immunohistochemically, there was strong staining for neuron-specific enolase, chromogranin, and low-molecular-weight cytokeratin as well as diffuse positive staining for glucagon. By electron microscopic study, characteristic intact α cell secretory granules were seen.

Conclusion: Such granules may be potential markers of malignant glucagonoma, in addition to the atypical granules described by others.

12. Polyclonal Light Chains in the Urine with Liver Disease: Case Report. Khurram Nazeer, Cecil Robertson, Hans W. Grünwald. Mount Sinai Services at Queens Hospital Center.

Background: Liver cirrhosis is frequently associated with reactive polyclonal hypergammaglobulinemia and plasmacytosis. However, re-

active urinary polyclonal (both kappa and lambda) free light chains have not been reported in liver disease.

Case Report: A 61-year-old man with a history of alcohol abuse was treated for multiple myeloma at another hospital with one cycle of melphalan and prednisone based on hypergammaglobulinemia, Bence-Jones proteinuria, and marrow plasmacytosis. Six weeks later he was admitted to our hospital with weakness and generalized swelling. He was reevaluated for his presumed multiple myeloma. On physical examination he had slight puffiness around the eyes. Chest was clear. The liver was palpable 2 to 3 cm below the right costal margin. The spleen was not palpable. He had anasarca.

Laboratory findings included white blood cells, 4100/ μ L; hemoglobin, 8.9 g%; hematocrit, 26%; platelets, 52,000/ μ L; prothrombin time, 15 sec; partial thromboplastin time, 37 sec; total protein, 6.6 g%; albumin, 1.6 g%; globulins, 5.0 g%; alkaline phosphatase, 100 U; bilirubin .3 mg%; lactic dehydrogenase, 250 U; ALT, 5 U; AST, 33 U; gamma glutamyl transferase, 65 U; cholesterol, 61 mg%; amylase, 140 U; urea nitrogen, 13 mg%; creatinine, 1.2 mg%; hepatitis B surface Ag neg, surface Ab neg, core Ab neg, hepatitis C Ab pos. Serum protein electrophoresis revealed a polyclonal (broad) pattern of hypergammaglobulinemia. Urine protein, 24 hour, was 1.2 gm, and on electrophoresis it migrated broadly in the beta region. Immunofixation of the urine revealed broad (polyclonal) bands of free kappa and lambda light chains. The bone marrow aspirate revealed normal cellularity with 25% plasma cells. Skeletal survey failed to show any lytic lesion. Chest x-ray was normal. Sonogram and CT scan showed hepatosplenomegaly.

Based on the polyclonal nature of the hypergammaglobulinemia and proteinuria, the diagnosis of multiple myeloma was ruled out. The alkylating agent was discontinued, and he was discharged with the diagnosis of alcohol- and hepatitis-C-induced liver disease with reactive hypergammaglobulinemia.

Conclusions: The reason for the previously undescribed excretion of large amounts of polyclonal free light chains in the urine remains unexplained, and we plan to do further studies in search of a defect of immunoglobulin assembly in this unique patient.

13. Crossed-Leg Palsy and Ambulatory Dysfunction in an Untreated 55-Year-Old Man with Juvenile Rheumatoid Arthritis. Shereef Girgis, Adolph Meyer, Nalini Paddu, Cheung B. Yui, Brian J. Rosenthal. Mount Sinai Services at Queens Hospital Center.

Published in Arch Physical Med Rehabil 1995; 75(9):1047.

14. An Unusual Presentation of Multiple Myeloma. R. Kahn, C. Brod-Miller, H. Grunwald. Mount Sinai Services at Queens Hospital Center.

Case Report: A 70-year-old black man with a ten-year history of hypertension was seen for routine follow-up. He was asymptomatic. On physical examination the pulse rate was 104 beats/min. No other physical findings were significant. His serum creatinine was 4.4 mg/dL and blood urea nitrogen (BUN) was 101 mg/dL. Three months earlier these values were 1.7 and 24, respectively. Urine protein, 24 hour, was now 1.2 grams. Kidneys were normal in size by ultrasound. Serum protein electrophoresis showed no paraprotein. Antinuclear antibody was negative and complement levels were normal.

Six weeks later the serum creatinine had risen to 9.7 mg/dL and BUN to 119 mg/dL. Free kappa light chains were found on urine protein electrophoresis. Bone marrow aspiration was diagnostic of multiple myeloma. Glomerular and tubular changes on renal biopsy were consistent with multiple myeloma. The patient is currently receiving four-drug chemotherapy and long-term renal dialysis.

Conclusion: Multiple myeloma should be part of the differential diagnosis of every patient with rapidly progressive renal failure.

15. Silicone Testicular Implants and Undifferentiated Connective Tissue Disease: Two Case Reports. Esther Lipstein-Kresch, Anwer Rasheed. Mount Sinai Services at Queens Hospital Center.

Background: Several reports in the literature show an association between breast silicone implants and the onset of connective tissue diseases. Spiera and Kerr (1) reported a cumulative experience of 11 cases of scleroderma following silicone implantation. Uretsky et al. (2) reported a patient with a severe systemic illness after breast implantation that improved after removal of the implants.

Case Reports: We report on two patients. One was a 52-year-old man with bilateral testicular silicone implants, postorchietomy for prostate carcinoma, who developed Raynaud's phenomenon, chronic arthropathy, and positive antinuclear antibody (ANA) 8 weeks after the implants. The second patient, a 39-year-old man with a testicular implant postorchietomy for testicular cancer, developed unexplained acute, recurrent attacks of incapacitating arthralgias and arthritis of the large joints that resolved after the implant was surgically removed. The second patient had normal laboratory parameters, including a negative ANA and a normal erythrocyte sedimentation rate.

Conclusions: It is possible that in both these patients, the clinical syndrome was induced by the silicone gel implant. In the second patient, removal of implants was associated with clinical improvement.

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THE



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Environmental and Occupational Medicine In Clinical Practice

Richard P. Wedeen, guest editor

From the Veterans Affairs Medical Center
East Orange, NJ

And the Departments of Medicine and of Preventive Medicine and Community Health
University of Medicine and Dentistry of New Jersey—New Jersey Medical School
Newark, NJ

THE MOUNT SINAI JOURNAL OF MEDICINE

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Introduction

RICHARD P. WEDEEN, M.D.
Associate Chief of Staff for
Research and Development
Veterans Affairs Medical Center
East Orange, NJ

Professor
Departments of Medicine and
of Preventive Medicine and
Community Health
University of Medicine and
Dentistry of New Jersey—
New Jersey Medical School
Newark, NJ

Environmental and Occupational Medicine in Clinical Practice

PRESENTING OCCUPATIONAL AND ENVIRONMENTAL MEDICINE to practicing physicians is a challenge. Were I considering that challenge from the perspective of my residency days, I would say it is most unexpected; during my training in nephrology at The Mount Sinai Hospital—under Marvin Levitt some three decades ago—nothing seemed more remote than occupational or environmental disease; in nephrology, tubular transport reigned supreme. Through the vagaries of clinical practice, my attention was later directed to occupational lead nephropathy. But occupational diseases appeared to be beyond the pale of nephrology. What had been learned about lead as a cause of kidney disease by Jean Charcot, Alfred Baring Garrod, and their colleagues in the nineteenth century had been all but forgotten (1). Forgetfulness driven by medical fashion was reenforced by the imperatives of the practice of medicine; prevention was peripheral. The etiologic relationship between chronic low-dose environmental exposure and later disease was difficult to discern at the bedside. Epidemiologic thinking had to achieve clinical respectability before preventive medicine could influence internists.

Lead poisoning provided my introduction to occupational and environmental medicine, an instructive starting point for examining the problems of etiology. Unlike most environmental hazards, the cumulative absorption of lead can be measured. Lead is accumulated in bone with a biologic half-life approximating twenty years, and 90% of the body stores of lead are retained in bone. Exposures long past and those unrecognized when they occurred can be documented by the EDTA lead-mobilization test and by the more recent noninvasive technique for measuring bone lead known as *in vivo* K-x-ray-induced x-ray fluorescence (XRF). On the effects of asbestos, Irving J. Selikoff convincingly demonstrated the health consequences of long-term low-dose exposure, a causal relationship easily overlooked at the bedside.

Reluctance to include environmental toxicology in the mainstream of medicine has weakened the authority of physicians in the great health care policy debates of our times. Relegation of responsibility for prevention to nonphysicians has alienated a public sensitized to environmental issues. The connections between bedside medicine and environmental policy remain the domain of polemic more than of science. Although the management of community and industrial wastes generates controversy, the exact nature and frequency of the adverse health effects of such wastes are only vaguely understood. Uncertainty about the effects of industrial hazards stems from a paucity of research in the area. Policy makers such as the National Institutes of Health have focused on reductionist science. The enormous cost required to measure in large populations low-level effects that may take decades to be manifest has made such studies unpopular in academic medicine.

The lack of evidence of adverse effects cannot, however, be construed as evidence for the lack of such effects, since no one has looked for the evidence carefully. But lack of information cannot prevent policy making. Inaction is also a policy and has consequences for the future: benefits accrue to those who save the cost of cleanup rather than to the public whose health remains in jeopardy.

Like the art of medicine, the art of public health is practiced without adequate information. But public policy can be either

more or less effective, even in the face of ignorance. Witness the use of quarantine before germ theory was established.

The dilemma remains unresolved because of lack of information on how much money could prevent how much disease. And physicians remain aloof to the controversy. This special issue of the journal explores the interfaces between internal medicine, occupational medicine, environmental medicine, and waste management, in the hope of increasing interdisciplinary dialog. Such dialog is rare among physicians, physicists, medical sociologists, engineers, and toxicologists, but still rarer between these experts and the communities they would serve. Here we attempt to bridge some of the gaps between specialists.

Occupational disease, disorders in a few workers exposed to high dosage over years, provides a first step in identifying the health impact on vast populations of low-dose environmental exposures. Occupational diseases present a bridge between clinical and environmental medicine through what have been termed "sentinel health events" (2)—clinical disease which stems from workplace exposures. But low-dose exposure may not simply cause less adverse effects than those that occur after high-dose occupational exposure. Threshold effects—toxic effects such as carcinogenicity that at very low exposure levels do not occur—may be operational.

In the face of inevitably inadequate data on the impact of environmental exposures on health, what should physicians do? Reassurance that risks are small is one approach. But perceptions of risk by experts and by those who are at risk often differ. Politicians who fail to see this difference do so at their peril. Reassurance offered without concrete data, in the face of deep-seated skepticism, is often counterproductive. Physicians and politicians alike are well advised to reassure less and to observe exposed subjects more. Long-term medical surveillance can answer questions about health effects in the future, and provide the best reassurance in the absence of hard data, reassurance that every effort is being made to monitor and to prevent adverse health effects.

This theme issue on environmental and occupational medicine attempts to broaden the dialog on environmental health. It begins with environmental controversies as they surface in communities. In "An Urban Community Faces an Environmental Hazard: 'Let Them Eat Chromium?'" Helen E. Sheehan, Ph.D., a medical sociologist, examines the responses of community activists in Jersey City, New Jersey, to the widespread distribution of chromium-contaminated landfill in

that urban community. The inability to find either a medical or a political solution to a perceived environmental threat created an all-too-common dilemma for the community. The second paper dealing with community responses to perceived hazards is "Effects in Society of Ionizing Radiation" by the Nobel Laureate Rosalyn S. Yalow, Ph.D. A physicist with unique expertise in the medical use of radioisotopes, Dr. Yalow brings her considerable talents to bear on public perceptions of the dangers of low-level radiation. Jenna S. Roberts and Ellen Silbergeld, Ph.D., next focus on the special biologic vulnerability of women to environmental hazards in "Pregnancy, Lactation, and Menopause: How Physiology and Gender Affect the Toxicity of Chemicals." Dr. Silbergeld is a neuroscientist, editor of the journal *Environmental Research*, and a spokesperson for the Environmental Defense Fund. David Wartenberg, Ph.D. provides an in-depth review of the controversy surrounding the carcinogenicity of electrical fields ("Health Risk Implications of Electrical Fields"). The potential dangers of electromagnetic fields was brought to public attention by Paul Brodeur in *The New Yorker* and remains in the public eye. Popular concerns have stimulated scientific attention.

The theme issue then focuses on toxic hazards and engineering responses. Philip J. Landrigan, M.D., M.Sc., Andrew C. Todd, Ph.D., and Richard P. Wedeen, M.D., provide a clinical update on lead poisoning. In this paper by a pediatrician, a physicist, and a nephrologist, the perspectives of the clinician and the public health official coincide. The paper by Michael Gochfeld, M.D., M.P.H., "Incineration: Health and Environmental Consequences," on the environmental fallout from solid waste incinerators, reminds us again of the gap between engineering and clinical medicine. Dr. Gochfeld wears the hats of clinician and policy analyst, but in this paper he examines pollution from the point of view of exposure limits rather than of the bedside. C. R. Krishna, Ph.D., R. C. Klein, Ph.D., K. W. Jones, Ph.D., and N. L. Clesceri, Ph.D., M.P.H., take the engineering point of view looking at the environmental contamination of the New York–New Jersey regional waterways in their article on human exposure to toxic materials in that area. This team of physicists and engineers believes that identifying regional problems is the first step toward finding technological solutions. The approach here is more geological than medical.

Next the theme issue looks at some of the sources of information about environmental toxicology and the distortions that can arise when

scientific debate is controlled by special interests. Richard P. Wedeen, M.D., provides a vignette in the history of lead poisoning. He shows how the Lead Industries Association effectively controlled lead research for 25 years—in its leaders' own words. Alice Stewart, M.D., has played a major role in describing the delayed effects of low-dose radiation in the Hanford Nuclear Plant in Washington State, and in the latent effects of diagnostic x-rays during pregnancy, on the induction later in life of cancer in exposed children. In her article in this issue, "Alternative Sources of Risk Estimates for Cancer Effects of Radiation," Dr. Stewart is concerned with conflicting interpretations of data on the late effects of low-dose radiation exposure in adults.

The final group of papers deals with the practical application of occupational medicine to medical teaching and practice. Arthur Frank, M.D., in "Medical and Public Health Approaches to Asbestos Disease," looks at the interface between epidemiology and clinical practice in the case of asbestos. A former student of Irving Selikoff, Dr. Frank incorporates both the public health and medical perspectives on asbestosis disease. Another of Selikoff's students, Elihu Richter, M.D.,

provides examples of how identification of sentinel health events merges occupational medicine with clinical practice in his and Paul Barach's article, "Occupation and Environment in Internal Medicine." Drs. Philip J. Landrigan and Dean Baker conclude with "Clinical Recognition of Occupational and Environmental Disease," a description of the integration of occupational medicine and clinical practice at the Mount Sinai School of Medicine.

Together, these manuscripts present a cross section of the state of the art of occupational and environmental medicine in clinical practice. The presentation is not intended to be comprehensive. Public and professional attitudes are changing so rapidly that the relationship of physicians to preventive medicine and public health is at best a moving target.

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An Urban Community Faces An Environmental Hazard:

"Let Them Eat Chromium"?

HELEN E. SHEEHAN, Ph.D.

SINCE THE 1960s, environmental hazards in American communities have become prominent public issues. Federal and state agencies and laws especially designated to deal with hazardous wastes have come into existence. Scientists and physicians determine the threat to human health that environmental hazards may create, decide about remediation of waste sites, and establish medical surveillance and treatment of exposed individuals. Oversight by public agencies, regulation by law, remediation by scientists, and treatment by physicians is a complex process. Often, the outcomes expected by the communities are neither adequate nor timely.

Communities dealing with the unexpected have to face the unknowns of the toxin—not only its effect, but in some cases even the location and extent of its dispersion. Uncertainty, therefore, is high. Anthropological studies, such as Malinowski's classic analysis of the use of magic by the Trobriand Islanders to control conditions when fishing far from shore or in bad weather (1), indicate that when people must deal with difficulty, with the unknown, the uncertain, they often re-

sort to magic, joking, and other rituals to assist them in coping. In our day, community members and the experts engage in rituals as well—the "expert" study, the "expert" remediation, the medical surveillance, community informational meetings—all of which serve to satisfy legal requirements and to provide reassurance that "something" is being done.

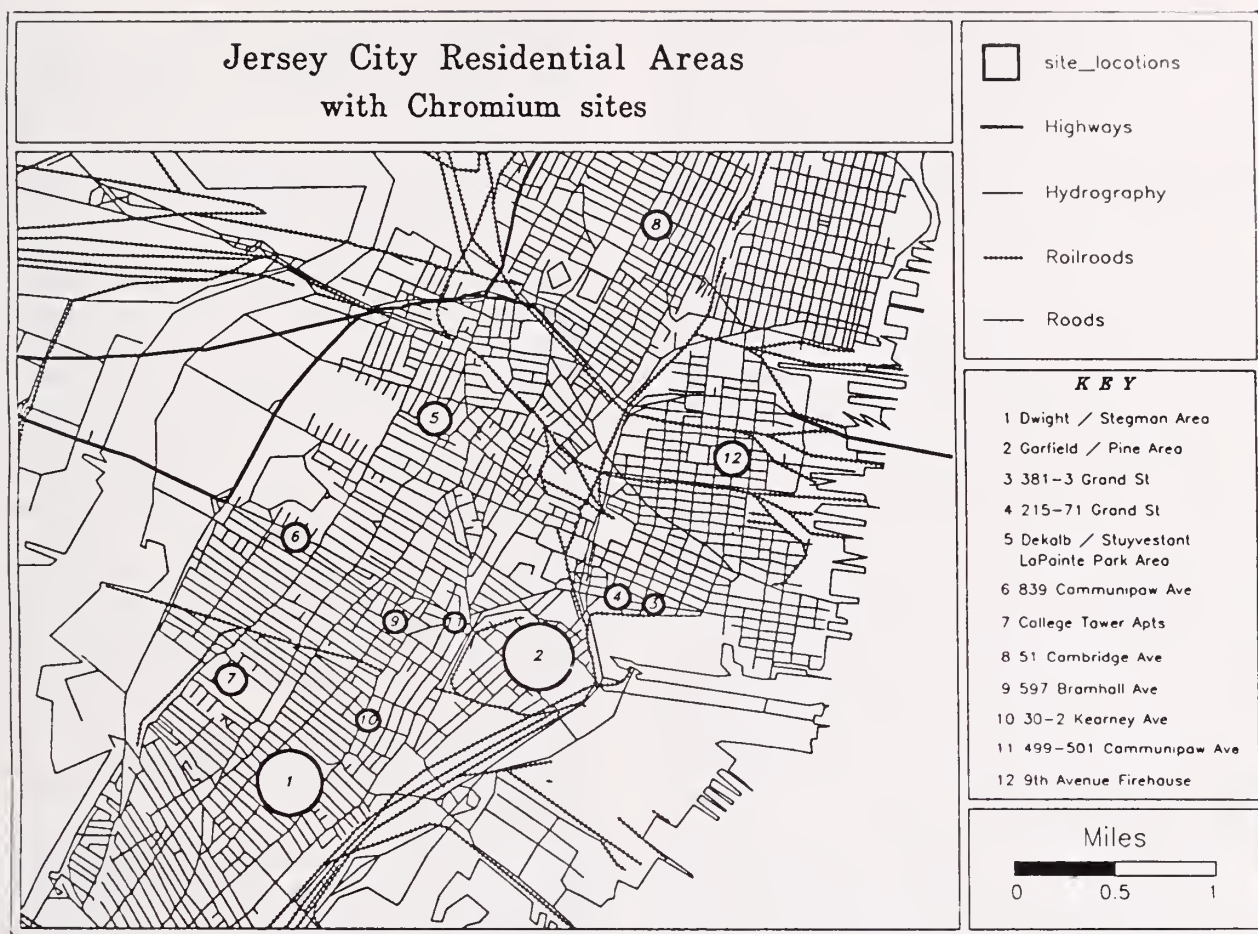
This paper reviews the interplay of institutions, agencies, experts, and community members in one case history of environmental contamination in New Jersey. The story is ongoing; the cast of characters changes as political administrations change. Promised official reports are often delayed or issued piecemeal. In other words, like many other environmental stories worldwide, resolution is rare. Vested political and corporate interests clash with community interests. In the case discussed here, the persistence of a community group, the Interfaith Community Organization (ICO), has frequently prevailed against powerful political and economic forces. Since 1976, state laws have supported remediation and medical screening of those exposed. The change in political administration in the state in 1994 may alter the outcome of the case.

The Chromium Hazard in Hudson County

Three million tons of chromium wastes, the byproduct of chromite ore production, are scattered throughout Hudson County, New Jersey's most urbanized and densely populated county. Jersey City, with a population of 230,000 (1990 census), the county's largest city and the state's second largest city, is home to the major portion of the waste.

Updated and revised version of "Is It in My Backyard?: The Chromium Waste Crisis in Jersey City, New Jersey," by Helen E. Sheehan, Ph.D., Richard P. Wedeen, M.D., and Iris G. Udasin, M.D., presented at the American Sociological Association, August 8, 1994, and of "A Sociological Analysis of the Roles of Government, Scientists, Physicians and the Community in Environmental Health," by Helen E. Sheehan, Ph.D., presented at the International Conference on Environment and Health in Developing Countries, Calcutta, India, December 16, 1994.

From the Department of Sociology and Anthropology, St. John's University, Jamaica, NY. Address reprint requests to the author at the Department of Sociology and Anthropology, 8000 Utopia Parkway, St. John's University, Jamaica, NY 11439.



Source: New Jersey Dept. of Health, 1990/1, "Chromium Medical Surveillance Project: Physician Training Manual"

Fig. 1.

How the Hazard Arose. From 1890 to the early 1970s, three Hudson County companies, two in Jersey City (PPG Inc. and Allied Signal, Inc.) and one in Kearny (Diamond Shamrock), processed chromate ore to produce chromium used in paint, stainless steel, chrome plating, photographic chemicals, and leather tanning. As a result, Hudson County became the second largest site—second only to Tokyo—of hazardous chromium wastes in the world.

Beginning in the 1950s, these companies sold and gave away chromium waste; the wastes were used for landfill throughout Jersey City and in other county towns (2). Indiscriminate and haphazard dispersal of chromium wastes in the 1950s resulted, by the late 1970s and continuing through the 1980s, in the discovery of these overwhelming wastes in playgrounds, ballfields, public buildings, businesses, private homes, vacant lots, and manufacturing plants. To date, 153 residential and nonresidential chromium waste sites have been identified in Jersey City (Fig. 1) (3).

History of New Jersey's Industrial and Environmental Protection in the State. Early in its history, New Jersey became home to industries such as pottery and glass making and to producers of oil and chemicals such as chromium. The state was among the first forced to address issues of hazardous waste production, occupational health, and, most recently, environmental health (4, 5).

By the 1970s, the New Jersey State Legislature began formulating environmental legislation, establishing a Department of Environmental Protection (DEP) in 1970. Most important for the chromium waste story, in 1976 the New Jersey Spill and Compensation Act, the model for the federal "Superfund" program (6), was passed.

The Spill Act, with amendments passed since 1976, "marked the beginning of the modern period of environmental law in New Jersey" (7, page 619). The act provides for a tax on the producers of oils and chemicals, which goes into a fund for hazardous waste cleanup; it also makes compa-

nies responsible for the costs of cleaning up hazardous sites. The law allows the DEP to proceed with cleanup of sites with monies already in the fund. If the companies identified as responsible for a hazardous site do not immediately provide funds for the cost of the cleanup, they are liable for charges three times the initial assessment.

By 1990, refinements of this law, as well as legal rulings on the intent and purpose of the act, made it unlikely that corporations would refuse the DEP's orders to clean up toxic sites. This law enabled remediation of chromium sites and health surveillance of people identified as having been exposed to chromium to be undertaken. Appropriation of funds for a feasibility study of Jersey City chromium cleanup procedures and for removal of chromium wastes in Jersey City were made in 1985 by the New Jersey Senate (8).

Management of the Hazard 1976–1994. Although the initial pattern of discovery and outcry about the chromium hazard in Hudson County echoes that of earlier environmental crises in the United States, such as Love Canal, New York (multiple toxics contamination) or Times Beach, Missouri (dioxin contamination), the management of the situation has differed.

The environmental legislation passed in New Jersey between 1976 and the present (7) enabled a process of accountability for remediation of the hazard and medical screening of residents to be established.

Moreover, chromium wastes are so ubiquitous in Hudson County that a multid denominational church organization, the Interfaith Community Organization (ICO), dedicated to community action against drugs and for safe, clean parks, became involved in the chromium crisis (and, subsequently, other environmental issues) when it could not identify a location in the county that was not chromium-contaminated in which to invest \$5 million to build low-income housing (9, 10).

The state's activities, and actions taken by the ICO to insure continued community input in the resolution of the chromium situation, have sustained chromium as a public issue since the late 1970s.

The Effect of Political Change: "Let Them Eat Chromium"? Since 1994, under the new political administration of Governor Christine Todd Whitman, discussion of changing standards has been taking place. One observer noted (11):

Under new proposals being discussed, the contamination level requiring a cleanup would be lifted so high that no site would be eligible for cleanup and the \$200 million dollars would be returned to the corporations. . . . the Whitman

administration would define the problem of chromium out of existence and the polluters would receive a corporate rebate at the expense of public health. . . . Is this the Whitman urban strategy: "Let them eat chromium"?

Lay and Scientific Understandings Of Chromium Exposure In Hudson County

As in all cases of toxic wastes, a primary question is what the health effects of exposure to the toxin are. The dangers of excess exposure to chromium in the workplace are documented in the medical literature (12). The Division of Occupational and Environmental Health of the New Jersey Department of Health issued a guide about chromium for Hudson County physicians in 1990 identifying the following health effects from chromium compounds (13, page 1):

- acute toxic poisoning from ingestion or skin penetration
- irritant and allergic effects on skin and membranes
- reversible renal tubular changes
- lung cancer associated with prolonged occupational exposure

The brochure notes that "clinical findings specifically associated with chromium exposure are nasal septal perforation and chromium skin ulcers" (13, page 2). The leaflet also states, "Effects from environmental exposure of the type occurring in Hudson County have not been studied" (13, page 1).

The information bulletin "Chromium and Your Health," issued by the DOH in 1989 (14) for the general public, presents information on the effects of high levels of exposures to chromium in the workplace. Other statements in the brochure are general in explaining how exposure can take place ("through the air by breathing in contaminated dust . . . by swallowing contaminated water, soil and food . . . by direct contact with the skin") (14, page 1). This brochure does not state, as the physician's guide does, that environmental exposure effects have not been studied. Depending on one's interpretation of the leaflet, one might conclude that any exposure to chromium is dangerous.

The local media developed a formula for presenting chromium's health effects, rarely including a distinction between occupational and environmental levels of exposure. Readers learned that there are two kinds of chromium—hexavalent and trivalent—hexavalent being the most worrisome because it is soluble, reactive with tissue, and easily absorbed into bodily cells (2, page

208). In a set style, the community press presented the list of diseases and symptoms identified with the toxin—"Exposure to chromium can cause kidney and liver damage, respiratory problems and skin ulcerations and has been linked to lung cancer" (15). Hence, residents, such as those in the Lafayette section of the city, were able to prepare "a list of ailing children [which] . . . is a litany of rashes, headaches and stomach pains"; one mother wrote of her daughter, "She runs fevers without having any cold," and another wrote, "One daughter has a rash on her leg; my son keeps getting sore throats and fevers and mouth sores" (16).

The nature of the risks of community-level exposure in the short and in the long term are unknown. A physician could find numerous causes other than chromium exposure for the ailments identified by the mothers. Measurement for chromium in the body can be done through urine or blood samples.

Social and Political Responses

Jersey City and Its Neighborhoods. The widespread presence of chromium wastes and the multifaceted social and political response to the chromium crisis is, in part, explained by Jersey City's physical layout. Beginning in colonial times, this land facing Manhattan across the Hudson River had many small settlements that were incorporated by 1873, creating the city as it is today (17, page 48).

As in many cities, residents identify strongly with their neighborhood. Thus, when chromium contamination began to be identified in various parts of the city, reactions by residents were by neighborhood—first relief that "it is not in my backyard," then anger and fear when "it is in my backyard" (18, 19). No neighborhood was spared by ethnicity, race, or income (Fig. 1); yet the affected neighborhoods did not unite to identify the wastes as Jersey City's problem (19–21). I discuss one neighborhood, Lafayette, and its experience with chromium.

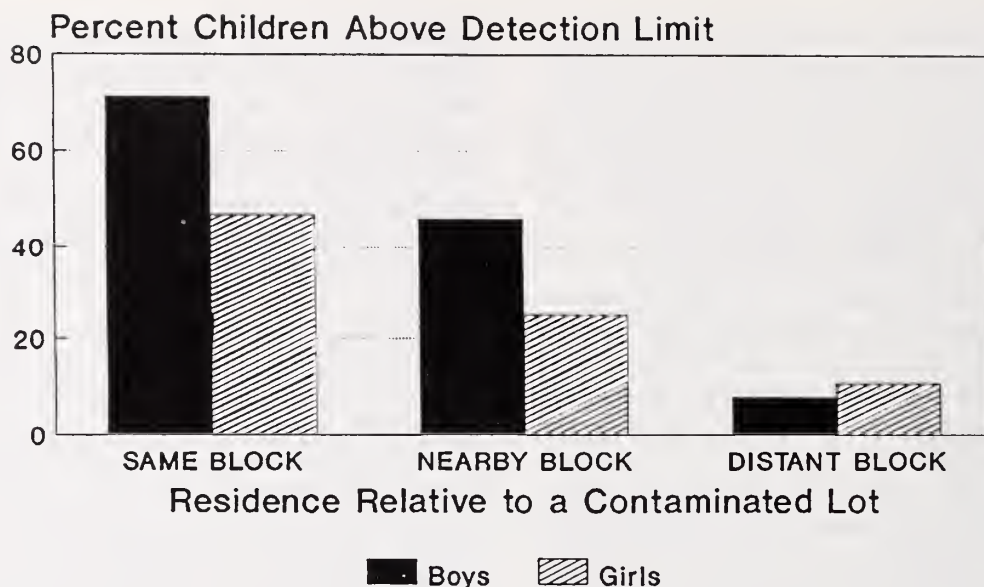
The Lafayette Area in Jersey City. In the Lafayette neighborhood is Public School 15 (the Whitney Young Jr. School), where yellow crystals and yellow dust appeared in the basement, leading to the identification of chromium wastes throughout the properties adjoining the school (2). Lou Manzo, then head of Jersey City's Department of Health, a critic of governmental handling of the chromium crisis and an activist in identifying sites, closed the school in May 1989. In the

following month, the Department of Health, using funds from the Spill Act, contracted with the Environmental and Occupational Health Sciences Institute to conduct the "Chromium Medical Surveillance Study" on 97 students and 68 staff members, subsequently published as "Medical Evaluation of Children and Adults of the Whitney Young Jr. School, Jersey City, New Jersey" (22).

One of the significant findings of this study is that students living on blocks where there were chromium sites had higher levels of chromium in their urine than did students living on nearby or distant streets (Fig. 2). The findings led the physicians and scientists involved in chromium exposure risk assessment to determine that a second study should be done of residents in the neighborhood surrounding P.S. 15 (23). An expanded medical surveillance study continued through 1993 with a total of 2,224 participants; 2,205 were examined by a physician. Of these, six persons were identified as having conditions in which chromium was suspected as "a possible cause or contributing factor." Among the six, four had skin conditions; three had nasal allergies (24, page 5).

In the community's view the release of the DOH final report (24) was unduly delayed. In June 1994, when it had not yet been released, a dramatic confrontation took place between the new head of the State Department of Environmental Protection, Commissioner Robert Shinn, and ICO members. Expecting a response about the medical surveillance study and plans for continued cleanup of chromium sites, the members instead found Shinn lecturing to them about types of chromium—a subject on which this group is well-informed (ICO, public meeting, Christ Our Saviour Lutheran Church, Jersey City, NJ, June 23, 1994). Whether because of the public embarrassment Shinn experienced at the group's refusal to continue to permit him to speak, or for other political or bureaucratic reasons, the ICO was informed that the study report had not been written and no date of release could be provided.

During the summer of 1994, ICO undertook a series of meetings with government officials about chromium contamination in Hudson County. In addition, in September 1994, ICO subpoenaed the Department of Health to release the report (25). At its next public meeting, on October 12, 1994, the ICO announced that it had obtained the promise of Gabriel Haytaian, a candidate for the office of U.S. Senator from New Jersey, to secure release of the medical surveillance report by October 15 (ICO, public meeting, Monumental Baptist Church, Jersey City, NJ, October 12, 1994). On



n = 97 children
Method Detection Limit = 0.3 ug/l

Source: New Jersey Dept. of Health,
1990/1, "Chromium Medical
Surveillance Project: Physician
Training Manual"

Fig. 2.

October 14, the Department of Health released the final report (24), with the summary results indicated above.

The outcome of ICO's strategies to gain release of the report, although a victory for the group and the community, leaves questions about the influence of politics in the functions of state departments designed to protect the public.

Role of the Interfaith Community Organization. The ICO is a member of the Industrial Areas Fund (IAF), a group of community organizations whose efforts are based on the ideas of the American organizer Saul Alinsky. ICO's fundamental interest is not the environment. The group's members identified chromium as a special concern when the ICO attempted to build low-income housing and was unable to find sites uncontaminated by chromium in the county.

Since 1989, ICO has developed a strategy of continuing interaction with the heads of state agencies concerned with chromium (the DEP and the DOH). ICO's objective is to have all chromium wastes removed. According to ICO strategists, the incumbents in the governor's office and in state agencies have their own agenda which may or may not coincide with the activities of and outcomes desired by the ICO. By maintaining contacts with officials and by maintaining a level of tension and confrontation during these contacts, the ICO strategy is to bypass official structures and bureaucratic rhetoric to achieve a goal—in this case, chromium waste removal and protec-

tion of the health of community members (personal interview, Tony Aguilar and Walter Bensman, June 13, 1994).

Because of its ties to the IAF, the ICO entered into the chromium crisis prepared with a more sophisticated and radical strategy than many grassroots organizations that have emerged out of environmental crises. It recognized the stigma that chromium created in the community (26); it realized that the state's interest in containing the crisis could be used by ICO to ensure total remediation; it came prepared to mistrust institutions and their spokespersons, an outcome usually found later in the history of environmental crisis (26).

Conclusions

The chromium waste problem in Jersey City represents complex scientific, medical, technical, economic, legal, political, and social challenges. Residents need respite from the continual disclosures of new sites, new evidence of governmental failure or ineptitude, new findings of residents or workers being exposed to chromium. How long can they worry every time the wind blows? The wind, after all, may contain chromium dust, as was pointed out by one of the early crusaders, Diana Crowder, industrial hygienist for Hudson Regional Health Commission (personal communication, 1992). The unknowns in the health effects of chromium exposure continually test profes-

sional skills in responding empathetically and honestly to individuals exposed to the toxin.

The commonalities shared by Jersey City's neighborhoods, as by other American urban centers—poverty, troubled schools, crime, drugs—are known; but measures undertaken by state and local government to address these problems are inadequate. In the chromium crisis, community members have found, especially in the medical surveillance project, attention to their problems. The state is mandated to address the issue of chromium exposure; thus chromium has become a symbol of government attentiveness that is not otherwise available. Clinical examinations and laboratory tests contribute little to resolution of community concerns, because rare abnormalities such as cancer are not apparent in small samples examined in the short term. Anxiety may be increased rather than decreased by medical attention. Nevertheless, medical and governmental experts have recognized that community anxieties over possible hazardous exposures cannot be quieted by unsubstantiated reassurance. Community concerns demand convincing efforts to obtain scientifically valid information. Such efforts include continuous long-term medical surveillance to document the presence or absence of postulated health effects of low-level long-term toxic exposure.

Now, a resolution phase of remediation and surveillance is being carried out by state bureaucracies—the DEP and DOH. State action is not a panacea. ICO activism on chromium has broken through the backyard fences to bring all Jersey City residents into social dialog about the community's involvement in the process of ridding the city of chromium wastes and preventing future environmental problems.

In the chromium story, as in other environmental histories, unchecked industrial activity left the community a troublesome legacy discovered many years later. This environmental story, like others, argues for a community voice in determining the nature of industrial development. By having meaningful input at the outset, communities will be able to ensure their future health and safety. Until such a process is commonplace, however, community vigilance and activism are essential to maintaining community environmental health.

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Effects in Society of Ionizing Radiation

ROSALYN S. YALOW, PH.D.

FEW SUBJECTS elicit more confusion than the popular perception of the hazards of exposure to low-level ionizing radiation and low-level radioactive wastes. Much of the public fear of radiation has been generated by the association of radiation and radioactivity with nuclear explosions and nuclear war. The American public is so phobic on this subject that the old dream of atoms for peace, including the use of nuclear reactors for power production, and even the use of radioactive materials in biomedical investigation and clinical medicine, is threatened.

It must be appreciated that radiation from natural sources has always been with us and is the principal source of radiation exposure for the general population. This exposure arises from cosmic radiation, from our self-contained radionuclides (the major component being the radioactive isotope of potassium, ^{40}K , with a half-life of 1.3×10^9 years) and from the natural radioactivity of soil and building materials. The average whole-body natural background radiation dose in the United States is considered to be about 0.1 rem per year. However, the yearly natural exposure can vary tenfold in certain regions.

Effects in Radiation Workers. There is no doubt that early radiation workers had a greater incidence of malignancies than do other groups. However, the extent of their excessive radiation exposure is not known. The classic picture of the

Curies working in their shed for four years while separating and purifying radium and polonium is one that will never be repeated. It is not surprising that Marie Curie died from aplastic anemia, probably secondary to the radiation exposure she received in her laboratory and during her experiences in World War I, when she personally provided X-ray services just behind the front lines, trained X-ray technicians, and installed 200 radiologic rooms. What is surprising is that she did not die until 1934, at the age of 66, in spite of cumulative exposures that must have been thousands of rems.

What is the radiation-related incidence of malignancies in more recent radiation workers with lesser exposures? A report (1) of the mortality from cancer and other causes among 1338 British radiologists who joined radiologic societies between 1897 and 1954 revealed that in those who entered the profession before 1921, the cancer death rate was 75% higher than that of other physicians, but that those entering radiology after 1921 had cancer death rates comparable to other physicians. The exposure of these radiologists was not monitored. However, it is estimated that even those who entered the profession between 1920 and 1945 could have received an accumulated whole-body dose of the order of 100 to 500 rem.

The exposure of those who were trained as radiology technicians and served in that capacity in the Armed Services for a median period of 24 months during World War II was not monitored. However, a description of their training included the statement that "during the remaining two hours of this period the students occupy themselves by taking radiographs of each other in the positions taught them that day" (2). These students did not receive a dose sufficient to produce

From the Veterans Affairs Medical Center, Bronx, NY, and the Mount Sinai School of Medicine (CUNY), New York, NY. Address reprint requests to the author, who is Solomon A. Berson Distinguished Professor-at-Large of the Mount Sinai School of Medicine and Senior Medical Investigator Emeritus, at Veterans Affairs Medical Center, 130 West Kingsbridge Road, Bronx, NY 10472.

skin erythema, nor did they show a drop in their white cell count—monitoring procedures that are insensitive to acute doses less than 100 rem. The cumulative exposures of these radiology technicians were not monitored. The radiation exposures of technologists at a more modern installation, Cleveland Clinic, were monitored in 1953 and found to be in the range of 5 to 15 rem/year (3). Army technologists a decade earlier probably received as much as 50 rem or more during their training and several years of service. Yet the 29-year follow-up of these 6500 radiology technicians revealed no increase in malignancies when compared with a control group of similar size consisting of Army medical, laboratory, and pharmacy technicians (4).

Effects of Natural Background Radiation.

Are there other more sensitive indicators of abnormalities, apart from malignancies, induced by increased natural background radiation? Such a study was performed in China by examining 150,000 Han peasants who had essentially the same genetic background and same lifestyle (5). Half of the group lived in a region where radioactive soil produced an almost threefold higher level of radiation exposure than that in the region of residence of the other half of the study group. More than 90% of the progenitors of the more highly exposed group had lived in the same region for more than six generations. The investigation included determination of radiation exposure by direct dosimetry and the evaluation of a number of possible radiation-related health effects, including chromosomal aberrations of peripheral lymphocytes, frequencies of hereditary diseases and deformities, frequency of malignancies, growth and development of children, and status of spontaneous abortions. This study failed to find any discernible difference between the inhabitants of the two areas. The authors of this study concluded that either there may be a practical threshold for radiation effects, or that any effect is so small that the cumulative radiation exposure to three times the usual natural background resulted in no measurable harm in this population after six or more successive generations. Similar studies in areas of high natural background radiation in Brazil and Kerala, India, have also reported negative results.

Effects of Diagnostic and Therapeutic Use of Iodine 131. Following the availability of radionuclides from Oak Ridge, iodine 131 was extensively used in the diagnosis and treatment of thyroid disease.

By 1968 an estimated 200,000-plus hyperthyroid patients had been treated with iodine 131 (6).

Since radioiodine remains the method of choice for definitive therapy of this disease, the total number so treated has probably doubled by now.

Thyroidal uptake of radioiodine was the method of choice for the diagnosis of thyroid disease until radioimmunoassay of thyroid-related hormones became available in the 1970s. An estimated 1 to 3 million people in the United States alone have received thyroidal doses in the range of 50 to 100 rems as a consequence of thyroidal uptake studies. There has been no systematic follow-up for radiation-induced malignancy in most of these several million patients. However, a follow-up has been reported of a small subset of these patients. Holm et al. (7) have reported a retrospective study of over 10,000 patients in Sweden who, for diagnostic purposes, received an average of 60 μ Ci iodine 131 and a thyroidal dose of about 60 rem between 1952 and 1965. Tracer studies were performed mainly on adults; only 5% of the patients were under 20 years old at the time of administration of the iodine.

The expected incidence of thyroid cancer in a control population of 10,000, according to data from the Swedish Cancer Registry, was 8.3, and only 9 were observed by Holm et al. (7). The mean follow-up period for the patients averaged 18 years, ranging from 10 to 25 years. The risk factors used by the United Nations Scientific Committee on the Effects of Atomic Radiation (9), derived from studies at high dose rates and from external X-radiation, predict an excess of 50 to 150×10^{-6} thyroid malignancies per person-rem within 25 years of radiation, with an equal number to be detected subsequently. Were this risk estimate valid, in the study group one would have expected an excess of 30 to 90 thyroid malignancies by 25 years—yet no excess was observed by 18 years. Since radioiodine thyroidal uptake studies have generally not been performed in nonhyperthyroid patients for more than a decade, it might be of interest to extend the studies of Holm et al. (7) to a larger fraction of the several million euthyroid patients receiving iodine 131 diagnostic tests in the earlier period.

Probably the largest group ever exposed to total body radiation in the 5 to 15 rem range were radioiodine-treated hyperthyroid patients. A study of 36,000 such patients from 26 medical centers, of whom 22,000 were treated with a single dose of the iodine and most of the rest with surgery, revealed no difference in the incidence of leukemia in the two groups (6). The average bone-marrow dose was estimated to be about 10 rems, more than half of which was delivered within one week. The follow-up for the group treated with

iodine 131 averaged seven years, quite long enough to have reached the peak incidence for leukemia, as had been determined from the Hiroshima-Nagasaki experience (8). A subsequent follow-up of the hyperthyroid patients three years later continued to reveal no difference in leukemia rates between the two groups (10).

This study emphasizes the importance of having an appropriate control group. Earlier studies had suggested that the occurrence of leukemia in hyperthyroid patients following iodine 131 therapy was 50% greater than that in the general population (11, 12). However, it appears from the study of Saenger et al. (6) that there is a 50% increased incidence of leukemia in hyperthyroidism, irrespective of the type of treatment.

Lung Cancer, Indoor Radon, and Cigarette Smoking. At present there is considerable concern about indoor radon. The concern was relatively minimal, however, until December 1984, when a worker activated the radiation alarms on entering Pennsylvania's Limerick nuclear power plant. The public then recognized that radon contamination in homes in the Reading Prong area of Pennsylvania—and perhaps elsewhere in the United States—might exceed levels currently permitted in mines. Subsequently the Environmental Protection Agency estimated that as many as 20,000 of the 140,000 annual lung-cancer-related deaths in the United States are due to home exposure to radon and its radioactive daughters. Is this estimate reasonable?

The rate of lung-cancer-associated deaths in the United States before cigarette smoking became common can be analyzed. On the basis of American Cancer Society statistics (13), in 1930 the male and female age-related annual cancer-related deaths rates were 4 and 2 per 100,000, respectively. By 1990, the rates had risen to 75 and 27 per 100,000, respectively. Because no sex-linked difference in lung cancer is anticipated, the 1930 rate for women probably approximated the actual cancer rate among nonsmokers. A pronounced underdiagnosis of lung cancer among women in 1930 is unlikely because the rate increased only slowly until 1960, when the effects of post-World War II smoking among women resulted in a continuously steeper increase in their lung-cancer-associated death rates.

Furthermore, in Utah the age-adjusted lung cancer incidence rate in the period 1967 through 1975 was only 4.7 per 100,000 among Mormon females and 27 per 100,000 among Mormon males (14). Because of religious beliefs, Mormons are supposed to abstain from smoking and the use of alcoholic beverages, and even from caffeine-con-

taining drinks such as coffee and cola. Although the incidence of lung cancer for Mormon males is less than half that for other American males during the same period, the findings suggest that not all Mormons abstain from smoking. Perhaps even some Mormon females are smokers or have been exposed to passive smoking. Underdiagnosis of lung cancer is unlikely in the Mormon community because they have excellent medical care. From these data, one might conclude that in the absence of smoking the lung-cancer-related death rate should be no more than 2 to 3 per 100,000.

The totality of evidence on radon suggests that, in the absence of smoking, radon does not represent a significant health hazard. Would the large sums of money needed for screening and testing for radon levels and for epidemiologic studies, which would predictably be nonconclusive, be better spent in other ways that would have greater impact on health? The question should be raised. Significant reductions in lung cancer deaths in 20 years would result only from significant decreases in cigarette sales now.

Conclusions

This brief review has been designed to emphasize that there are no reproducible studies that unequivocally demonstrate harmful effects of radiation delivered at low doses and dose rates. The question whether there exists a threshold below which radiation effects in humans do not occur should continue to be addressed. There is no doubt that in the case of biologic effects of low-level radiation, public policy decisions are increasingly being made on exaggerated estimates of potential harm. A statement in the National Council on Radiation Protection Report No. 43 on radiation protection philosophy is relevant: "Undue concern, as well as carelessness with regard to radiation hazards, is considered detrimental to the public interest (15)."

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Pregnancy, Lactation, and Menopause:

How Physiology and Gender Affect the Toxicity of Chemicals

JENNA S. ROBERTS AND ELLEN K. SILBERGELD, PH.D.

Abstract

We explore ways in which biological events and nonbiological gender factors in women's lives can mediate the toxicity of chemicals to women. We examine the physiologic changes that accompany pregnancy, lactation, and menopause in order to discuss how these changes might influence the target organ dose and distribution of toxic chemicals within women's bodies. We suggest that the interactions between divalent metals and calcium metabolism and those between lipophilic chemicals and fat metabolism could modulate the toxicity of metallic and lipophilic toxins in women over the course of a lifetime. These hypotheses need careful research consideration.

GROWING NATIONAL ATTENTION to health issues specific to women has included interest in environmental health, which has raised questions about the role of environmental factors in adversely affecting the health of women. Instead of taking women as the subject and looking at all the ways the environment has an impact on disease in women, research tends to focus on the ways in which environmental factors cause disorders unique to women, disorders more prevalent in women, and disorders caused by the reproductive and developmental effects of exposure to specific environmental hazards. This research seeks to define ways in which women are uniquely susceptible, or more susceptible than men, to the harmful effects of environmental toxins. These questions have captured scientists' imaginations, and many are rightly eager to fill in gaps in knowledge.

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From the Environmental Defense Fund (EKS, JSR), Washington, D.C., and the Department of Epidemiology and Preventive Medicine (EKS), University of Maryland Medical School, Baltimore, Md. Address reprint requests to Ellen K. Silbergeld, University of Maryland Medical School, Dept. of Epidemiology, 660 West Redwood St., Howard Hall 102A, Baltimore, MD 21201-1596.

Biology and Discrimination. At the same time, research on biological differences between men and women creates a legally treacherous ground because biology has often been used to justify discrimination. These legal issues must be discussed and examined along with the science, and they make the articulate and specific formulation of research questions crucial.

In some instances, purported differences in the toxicologic response of men and women have been used by advocates of more stringent environmental and occupation health regulation, as in Bern's concept of the "fragile fetus" (1). However, these data have also been used to justify policies of discrimination, specifically in employment opportunities in industries where toxic chemicals are used. Although a Supreme Court decision in the landmark case *UAW v Johnson Controls* in 1992 forbids a specific instance of such discrimination in hiring, that decision has had little impact on women's opportunities for employment (2).

Current legal doctrine allows discrimination on the basis of sex if a characteristic that affects an individual's ability to do a job is also associated with sex; such a characteristic is identified in law as a "bona fide occupational qualification." Seemingly neutral policies with discriminatory

impacts (called "facially neutral") are allowed for a "business necessity." Definitions of both defenses have been extensively argued. Industry has claimed that the "bona fide occupational qualification" supports what they term "fetal protection policies," which exclude fertile women from jobs in order to prevent exposure to chemicals alleged to be uniquely or specially toxic to the fetus (3). In the landmark case *UAW v Johnson Controls*, in which exposure to lead was at issue, the Supreme Court rejected the defendant's assertion that discriminatory hiring policies fell within the concept of a "bona fide occupational qualification." Nevertheless, employers have continued to express concerns over their potential liability for injuries sustained by an employee's child exposed prenatally, and debate continues on what constitutes a legally allowable impact of sex on job performance. Little effective effort has been devoted to developing nondiscriminatory alternatives such as reducing exposures so that everyone in the working population is equally protected to a maximum allowable level of risk.

Sex and Gender in Differential Susceptibility

Because of the implications for discrimination, careful scrutiny of claims about the biological basis of different susceptibility, and therefore risk for disease, is of utmost importance in discussing environmental and occupational risks. Women and men are different as a result of genetics, but also as a result of different social and cultural positions, both of which may affect biology and health. Furthermore, biological differences do not necessarily imply differential risk by sex as a class. For example, although the averages for a given biological parameter may be different for men and women taken as a whole population, values for particular parameters in individuals of each sex overlap considerably, as in such variables as body weight, fat content, and muscle strength.

The scientific literature indicates that certain diseases are more prevalent in women than in men. As a first step in examining prevalence, one must distinguish between those diseases in which the differential adverse affect may be related to biological differences and those in which sex is highly correlated with another extrinsic, nonbiological factor—a factor of gender rather than of sex—that is mediating differences in prevalence of the disease by sex.

Nonbiological factors of gender that are correlated with higher environmental exposures for

women include the following:

- poverty and socioeconomic status
- nutritional deficits, related to poverty or to eating behavior such as cyclical dieting
- occupational selection biases that favor women, as in nursing or housecleaning

Each of these factors can differentially increase women's exposures to toxicants. Selection bias that favors men, for example in chemical manufacturing jobs, may work in the other direction, to decrease women's exposures overall and therefore give the appearance of a lesser susceptibility to a given disease in women.

Age-related diseases may also be more prevalent in women than in men, but the sex difference may be related not to differential susceptibility but to the fact that a greater percentage of women survive to very old age (>85 yrs).

Sex Bias in Research. Sex bias in research can also inappropriately suggest that women have a higher biological vulnerability than men do. For example, the general perception that reproduction and fetal health are exclusively women's health issues has resulted in a lack of investigation of male-mediated reproductive toxicity. Male reproductive systems are also vulnerable to toxicants, and men's exposures can affect their offspring (4). Genotoxins that affect the gametes prior to fertilization may have similar reproductive effects in men and women. Much less research currently exists on male-mediated developmental toxicity than on female-mediated toxicity, primarily because of biased research and toxicity-testing designs (5) as well as difficulties in ascertaining paternal exposures and their relationship to developmental outcomes (6). For instance, concern over alcohol- and drug-induced deficits in infants has usually assumed that only maternal abuse can affect the child, despite the fact that many women who are substance abusers have partners who are also abusers. Too often, information on paternal co-exposures are simply not collected; for instance, as acknowledged by Bellinger and Needleman (7), none of the prospective studies these researchers examined on pre- and post-natal lead exposure and early infant outcomes even ascertained paternal lead exposures. Yet experimental studies have reported that paternal exposures to alcohol, morphine, and cocaine can affect the neurobehavioral development of offspring (8).

The Classic Conceptualization of Environmental Risks to Women. It is also common to conceptualize environmental risks to women's health as the effects of toxicants on sex-specific

TABLE 1
Physiologic Changes during Pregnancy

Parameter	Change	Potential implications for toxicology
Extracellular volume	↑ 4–6 L	Dilution of substances in circulation; redistribution of ions that follow calcium homeostatic mechanisms
Plasma volume	↑ by 40%	Same
Plasma renin/aldosterone	↑ ↑	Renal retention/excretion
Renal blood flow	↑ 30–50%	Same
Glomerular filtration rate	↑ 30–50%	Same
Sodium & calcium retention	↑ ↑	Retention of other divalent cations
Cardiac output	↑ by 40%	Increased sensitivity to cardiotoxins(?)
Increased blood flow to skin	↑	↑ Dermal uptake
Pulmonary hyperventilation (↑ tidal volume)	↑	↑ Inhalation dose
Food intake	↑ 70 kcal/day (average)	Increased dose
Energy demand*	↑ ~300 kcal/day pregnancy <i>fetal</i> <i>energy cost</i> : 560 g fat 420 g protein	Increased dose and metabolic shift
Lipid stores*	↑ ~3.4 kg over pregnancy (including fetus)	Same
Tissue oxygen consumption*	↑ 51 mL O ₂ /min (15 mL/min in breast during lactation)	Metabolic shift(?)
Basal metabolic rate	↑ 13%	Metabolic shifts
Hepatic triglyceride synthesis & secretion	↑	Redistribution
Femoral adipocyte mobilization (also during lactation)	↑	Redistribution

* Dependent on nutrition, activity levels, and gestational stage.

Adapted from data in ref. 15.

aspects of women's anatomy and physiology and on fetal growth. In a recent National Institutes of Health report on research needs in women's health, only the section on reproduction mentions environmental toxicants, in the context of fetal growth (9). Pregnancy, lactation, and menopause, normal stages of many women's lives, are biologic events unique to women. These stages can be affected by exposure to toxic chemicals. As understood classically, toxic chemicals can reduce fertility and increase the risks of spontaneous abortion; they can cause reproductive tract cancers; they can interfere with lactation; and they may lower the age of menopause (10, 11). Women may also be the physiologic source of toxic chemical exposures to their children during two of these stages—pregnancy and lactation (12, 13).

Physiologic Stages in Women's Lives. However, in this paper, we focus on a different aspect of the issue of environment and women's health. We ask how changes in women's physiologic states modulate the level of risk to women for diseases that may otherwise be similar in men and women. What, if any, of the physiologic aspects of pregnancy, lactation, and menopause can affect how women respond to toxic chemicals? What characteristics of toxic chemicals make this interaction likely to occur? We focus on these three periods in women's physiologic lives, preg-

nancy, lactation and menopause, and ask how changes in metabolism and other events could interact with the distribution and target site dose of various toxicants and result in differential toxicity to women. Our analysis suggests specific adverse outcomes and types of toxic substances that need to be investigated for differential toxicity.

Physiologic Changes in Pregnancy, Lactation, and Menopause

In this section, we review some of the major physiologic changes that occur during pregnancy, lactation, and menopause, with a particular emphasis on bone and fat metabolism. These three life stages are associated with many significant physiologic events, but bone and fat have been highlighted because these compartments often store and accumulate toxic chemicals and because there is information on the storage of bone-seeking metals and lipophilic compounds that is sufficient to suggest that changes in physiology are likely to modulate the risks of these chemicals, as discussed in the section that follows this one.

Pregnancy

Pregnancy is a period of significant physiologic change for women (Table 1). Blood volume

increases substantially (about 40% by the end of gestation); body composition changes and weight increases; food intake needed and intermediary metabolism change; absorption and retention of specific nutrients and minerals changes; the kinetics of hematopoiesis change; and immune system function is modulated (see generally 14; 15).

Changes in hormone levels and metabolism are likely to control many of these physiologic events. Estrogen levels fall and then rise later in gestation (estradiol decreases, estriol increases); levels of glucocorticoids and mineral corticoids rise, as do levels of thyroxine, insulin, progesterone, parathyroid hormone, and placental lactogen (15). The bone-related hormone osteocalcin declines, while 1,25-dihydroxyvitamin D and calcitonin increase (16).

Many of the physiologic changes relate to an increased demand for energy, oxygen, and specific nutrients such as calcium. As a woman's blood volume increases, the total amount of circulating calcium must also increase in order to avoid hypocalcemia—a condition of severely lowered circulating calcium, which affects muscle function. Both gut absorption and renal retention of calcium shift to favor increased availability of calcium in the circulation (17). Changes in hormonal status—especially increases in glucocorticoids and progesterone, as well as reductions in circulating levels of estradiol—also play a role in handling the calcium stress of pregnancy. Decreased estradiol signals bone cells to enter a state of relative resorption, whereby mineral is released from bone into the circulation (18).

Calcium Stress. The calcium stress of pregnancy can be considered in two phases, related to early and late stages of gestation. During early gestation, approximately the first half to two-thirds, the determinative physiologic conditions are primarily the reduced synthesis and release of estradiol and the increases in blood volume (Fig. 1) (19). During late gestation, particularly during the last trimester of pregnancy, a primary physiologic factor is the ossification of the fetus. During this period, the fetus requires about 30 gm calcium to support bone growth. Obviously, all of this calcium must be derived from the maternal circulation. During this phase, calcium absorption and retention changes, which is accomplished by changes in vitamin D metabolism and renal handling of calcium as well as by changes in the hormones thyroxine, calcitonin and, later, prolactin (see Fig. 2; 18, 19).

These stresses on the maternal supply of calcium can be met by two sources other than dietary increases: kidney and gut adjustments fa-

voring calcium absorption and retention, and the internal store of calcium in bone. Both events appear to occur during pregnancy. Moreover, it appears that if dietary calcium is insufficient, the draw on bone is increased. Under conditions of significant deficiency of dietary calcium, measurable osteopenia—loss of bone density—occurs (discussion, ref. 19). At the same time, even increased dietary calcium cannot completely prevent bone mobilization. Under conditions of dietary insufficiency or when other conditions prevail, such mechanisms may be marked, but they appear to be activated in well-fed, healthy women, indicating that hormonal controls are not completely suppressed by increased dietary calcium intake (20). This may suggest that human evolution has led to a strategy of physiologic conservation through hormonal signalling, relying on internal stores to meet the mineral demands of reproduction and to guarantee a sufficient supply of calcium for fetal development.

Copper, Zinc, and Cadmium. Pregnancy-related changes in mineral metabolism may also involve other organs of storage. Copper and zinc are required by the fetus during intrauterine growth, and much of this fetal demand appears to involve mobilization of copper and zinc from liver and kidney. Suzuki et al. (63) found that cadmium, which is stored in kidney and liver by binding to a copper and zinc binding protein (metallothionein), is not mobilized, which results in higher amounts of cadmium relative to the protective elements zinc and copper.

Energy Demands. The placenta and fetus also impose substantial energy demands on a pregnant woman, which changes her metabolism. During early pregnancy, both body fat stores and circulating plasma lipid levels gradually increase. Specifically, triglyceride and cholesterol levels increase, and low-density lipoproteins (LDLs) and very-low-density lipoproteins (VLDLs) become enriched in triglycerides (review in 21). For example, VLDL triglyceride and cholesterol content increase 2.5-fold during gestation to peak at parturition. VLDLs function as the primary carrier of triglycerides in the plasma, and their plasma concentration increases exponentially during the last trimester of pregnancy. In contrast, high-density lipoproteins (HDLs) peak at mid-gestation, with a 45% increase, and then fall back to about 15% above baseline. The ratios of proteins within the lipoproteins also change during pregnancy.

In late pregnancy the process of energy storage is reversed to support fetal growth. Several sources may contribute to the hypertriglyceri-

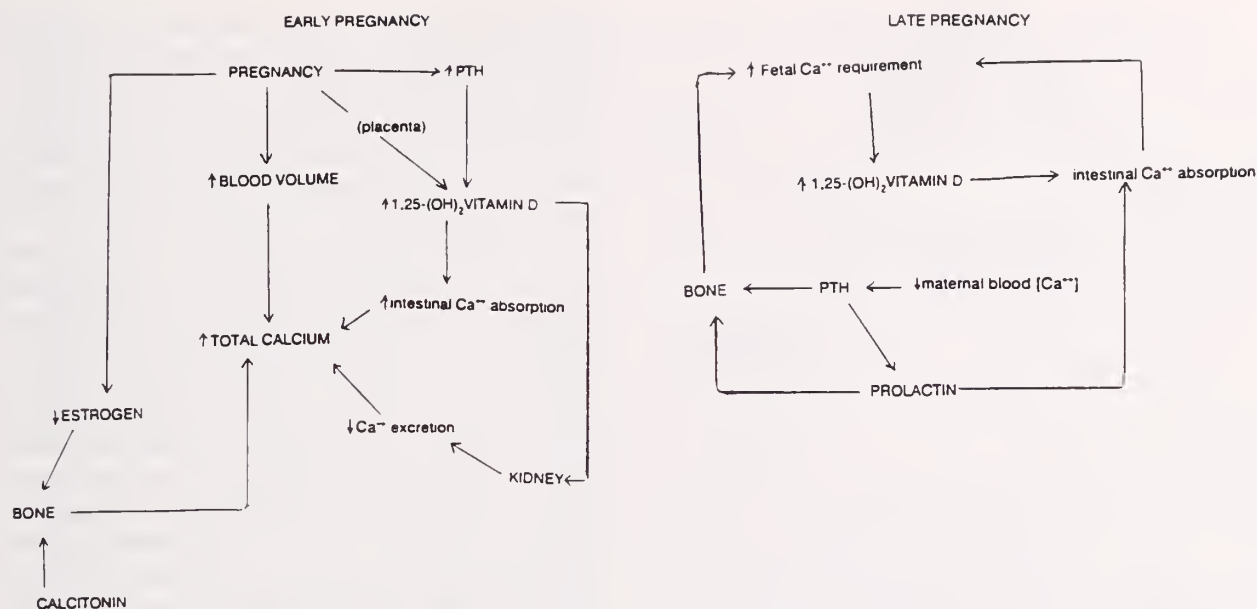


Fig. 1. Left Calcium metabolism in early pregnancy (first and second trimester). Because of increase in maternal blood volume, total calcium in blood compartment is increased primarily by increased intestinal calcium absorption and reduced renal calcium excretion. Decreased production of estrogen in pregnancy may also affect bone cell status through estrogen receptors, as observed in postmenopausal osteoporosis, that is, to increase bone resorption. The major hormonal signals governing these changes are parathyroid hormone and 1,25-dihydroxyvitamin D, both increased in circulation. Reprinted with permission from ref. 19. Fig. 2. Right Calcium metabolism in late pregnancy (third trimester). Fetal ossification becomes a driving factor in altering maternal calcium metabolism. Calcium is supplied to the fetus, and maternal calcium metabolism is regulated by vitamin D, parathyroid hormone, and prolactin. Reprinted with permission from ref. 19.

demia of pregnancy. First, more VLDL is released from the liver, seemingly without change in uptake and catabolism. Increased lipolysis in adipose tissue releases fatty acids into plasma to support increased triglyceride synthesis in the liver (21, 22). Decreased gastrointestinal tract transit times combined with normal lipid absorption rates increase the uptake of triglycerides through the diet. In late gestation, decreased storage activity in adipose tissue may also contribute to the increases in circulating lipids, although results vary between species (22, 23).

Although the mechanisms underlying these changes in humans are not known, in part they may be driven by hormonal changes. Studies of oral contraceptive users show changes in plasma lipid composition similar to those accompanying pregnancy, reflecting an enrichment in triglycerides (21). Knopp (21) suggests that these shifts in fat metabolism allow the maternal energy need to be met while preserving glucose to meet fetal energy needs, since triglycerides do not seem to cross the placenta as easily. Later in gestation, the high triglyceride level may be anticipating the needs of milk synthesis.

Lactation

Lactation is another period of substantial physiologic adjustment to meet the continued nu-

tritional needs of the newborn. As during pregnancy, in lactation the hormonal changes affect many organs, including mammary gland maturation, ovarian function (suppressing ovulation), liver and gastrointestinal tract handling of nutrients, and bone and adipose cell metabolism. Lactation may put more stress on body calcium and fat stores than pregnancy does. Continued fetal bone growth requires large amounts of calcium. Levels of osteocalcin are higher during lactation than during pregnancy or other periods (16). In rodents, measurable decreases in bone mineral content can occur during lactation (24).

Triglycerides are a major component of breast milk. Breast tissue synthesizes some of the needed triglycerides from glucose (also the precursor for lactose), and some are supplied directly from the diet or through increased hepatic synthesis from fatty acids. The relative importance of mammary and hepatic synthesis may vary with diet, since in rats, a high-fat diet decreases the utilization of glucose (25). Lipoprotein lipase (LPL) activity goes up in the breast tissue, allowing the cells to take up lipids from plasma. In fat cells, lipid release (lipolysis) increases while lipid storage decreases, thereby mobilizing fatty acids into the plasma (26). Interestingly, in nonpregnant and early-pregnancy women the femoral adipocytes are more active in storage, exhibit lower

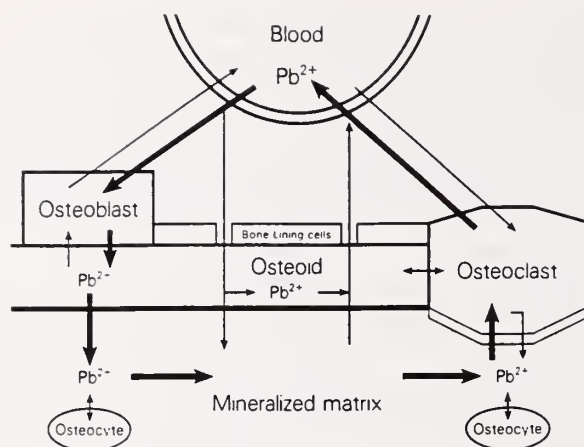


Fig. 3. Lead dynamics in bone. Reprinted with permission from ref. 37.

basal lipolysis rates, and are less responsive to the lipolytic effects of epinephrine (which mobilizes fatty acids) than are abdominal cells (26). During lactation, these femoral adipocytes become highly active, releasing stored fat, and are as responsive to epinephrine as are abdominal cells. This indicates physiologic differences between these adipocyte deposits in the utilization of stored fat for milk production and for meeting general, everyday energy needs.

Menopause

The cessation of reproductive fertility in women occurs when the supply of oocytes for ovulation is depleted and estrogen levels fall. The menopausal transition precedes ovarian depletion and is signalled by increased circulating levels of follicle-stimulating hormone and decreased estradiol. Symptomatically, many women experience a range of effects (such as hot flashes) and physiologic changes. Many of these changes have been related to the decrease in circulating estradiol, since the changes have been measured in women who have undergone hysterectomy and oophorectomy and can be reversed by hormone replacement therapy (27). These hormonally mediated changes affect a number of target organs and change women's health status in several ways. Of concern in this review are the menopausal changes in bone physiology and fat metabolism.

Bone Density. One of the most significant changes in women's health status associated with the menopause involves the density and strength of bone. Women lose bone density at a relatively rapid rate in the first five years after menopause. In some women who enter menopause with re-

duced bone density, this demineralization can significantly increase risk of fracture (28). Postmenopausal osteoporosis is a condition of severe bone density loss that affects between 10% and 15% of all postmenopausal women; it is a leading risk factor for bone fracture and premature death associated with loss of mobility (29).

Fat Metabolism. Fat metabolism also changes during the menopause. Perhaps most strikingly, the risk of several diseases associated with lipid or carbohydrate metabolism disorders increases with menopause, including cardiovascular disease, diabetes, and hypertension (30). Women experience a shift in the distribution of stored fat: the subcutaneous store decreases and visceral fat, around the abdominal organs, increases (31). This shift is significant because blood lipid disorders and blood pressure seem to correlate more with fat storage pattern than with overall obesity.

Blood cholesterol levels also increase with menopause, LDL rising most over the long term, although triglyceride levels remain relatively constant (32). There are suggestions in the literature that hormones are responsible for these changes because similar changes in blood lipid levels also occur after oophorectomy (33), whereas modern hormone replacement therapy, which combines estrogens and progestins, seems to reverse or prevent them (34).

Toxic Chemicals and Changes in Women's Physiologic Status

The discussion above suggests that toxic chemicals that are retained in bone and fat, normally considered slow-turnover, long-term storage sites, may be substantially redistributed in women during pregnancy, lactation, and menopause. The storage of bone-seeking elements may be changed primarily by the mobilization of bone calcium. Lipophilic chemicals, those taken up and stored in fat, may also respond kinetically to changes in fat uptake, retention, and mobilization.

Bone-Seeking Toxicants

Several metals behave like calcium in terms of compartmentalization in the body (35). Among these, lead, cadmium, aluminum, and mercury are of toxicologic significance.

About 90% of body lead stores are found in bone (36). Lead is taken up, retained, and released by bone cells under the same hormonal and

other influences as is calcium (Fig. 3). Lead has also been localized in the hydroxyapatite matrix of bone cells in an amorphous structure, substituting for as many as two calcium atoms per hydroxyapatite lattice molecule. In vitro studies of bone cells (from the line ROS 17/2.8) in culture have shown that the same hormonal signals that control calcium influx and efflux—calcitonin, parathyroid hormone, and vitamin D—govern lead (37).

Cadmium is also stored in bone, although not preferentially as is lead (35). In the Japanese epidemic of dietary cadmium poisoning, the most severe symptoms were reported in the postmenopausal women, suggesting that bone stores of cadmium were released at that time. Recent measurements of bone in vivo, using x-ray fluorescence technology, have found measurable concentrations of aluminum and mercury in tibia (McNeil, personal communication). It is not known whether this mercury is bio-available. Aluminum is accumulated in and toxic to bone. It may be released during conditions of demineralization, such as during renal dialysis (35). Although most of the available information relates to lead, because of its public health significance, that information on lead may be applicable, at least qualitatively, to these other toxic metals.

Most of the body's burden of lead is found in bone because lead is stored in bone with a long half-life, in excess of 10 years (36). Lead concentrations in both cortical and trabecular bone increase with age, although in old age these increases are blunted (38). Because of this, bone lead is a useful biomarker for chronic, integrated exposure (39). At the same time, the bone lead pool is dynamic, and circulating lead is largely supported by bone lead, creating a dynamic equilibrium that has been observed in those with high occupational exposures (Smith, personal communication; 40).

Bone lead also responds to changes in external lead exposure and to physiologic variables, including the life stages of pregnancy, lactation, and menopause. In particular, calcium stress induces a loss of bone density through the efflux of calcium. As far as is known, osteoclasts and osteoblasts treat lead (and possibly other toxic bone-seeking metals) analogously to calcium in terms of uptake, retention, and release (37). Moreover, the hormonal signalling systems that control bone mineral metabolism are apparently "blind" to whether lead or calcium is evoked.

Pregnancy. During pregnancy, bone stores of lead decrease in rats, supporting an increase in

TABLE 2
Levels of Lead in Blood in Women by Age

Dataset	Age range	Blood lead*
Hense et al. (1992)	30–39	6.3
	40–49	6.5
	50–59	8.9
Staessen et al. (1992)	28–37	6.0
	38–47	6.3
	48–57	6.9
NHANES II		
(Silbergeld et al. (1989)	Premenopause	11.6
1976–1980	Postmenopause	14.2†
NHANES III		
(Brody et al. 1994)	20–49	1.66
1988–1991	50–69	3.01

* Geometric mean blood lead levels, $\mu\text{g/dL}$.

† Postmenopausal nulliparous women only.

Reprinted with permission from Zelikoff et al., 1995, ref. 44.

blood lead levels (24). One study in women with uneventful pregnancies and normal babies at delivery found that after an initial decrease, levels of lead in blood rose during the second and third trimesters (41). In fact, lead in bone can be mobilized to the extent that women with high stores from prior exposures have become symptomatically lead-intoxicated in late gestation, and their children can have high lead levels in blood at birth (42).

Lactation. Similarly, lactation continues to mobilize bone lead, presumably along with continuing calcium mobilization. Watson and Silbergeld (24) found that lactation further blunted the age-dependent increase in stored bone lead and also greatly increased blood lead levels in rats. These events were discernible in rats exposed to lead via drinking water and also in animals not deliberately exposed. A recent report by Manton et al. (43) also found substantial mobilization of bone lead in women during breast-feeding.

Menopause. In women, there is inferential evidence for mobilization of lead in bone during menopause. Three separate studies (Table 2) have all found that blood lead levels in women increase over the period of time when most women cease ovulating, from age 35–45 to age 45–55 (44). These data are striking because similar age-related increases were observed among populations with very different levels of lead exposure: in the NHANES II national U.S. population survey from 1976 to 1980, median blood lead levels in adult premenopausal women were 11.6 $\mu\text{g/dL}$; in the NHANES III survey from 1988 to 1992, median blood lead levels were about 2 $\mu\text{g/}$

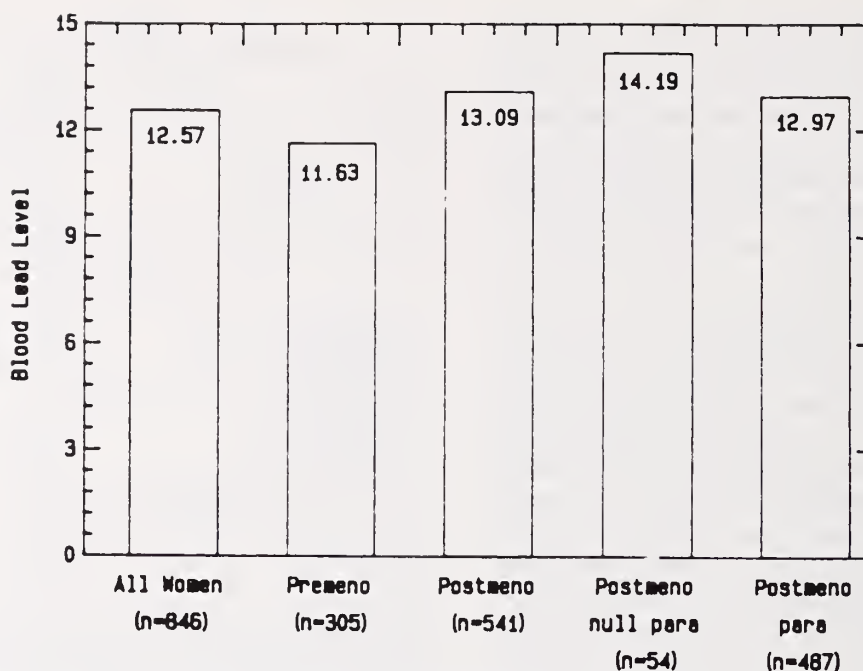


Fig. 4. Blood lead concentrations in black and white women, aged 40 to 60 years (n, numbers in sample used for analysis). Premeno, premenopausal women; postmeno, postmenopausal women; postmeno null para, postmenopausal women with no prior pregnancies; postmeno para, postmenopausal women with at least one pregnancy. Data from NHANES II survey; see Silbergeld et al. (17) for details of analyses. Reprinted with permission from ref. 19.

dL. Given that postmenopausal women are at higher risk for osteoporosis than men, if lead and calcium are handled similarly we might well expect that women are also likely to mobilize more bone lead more rapidly into the blood. In fact, the trajectory by age of women's level of lead in blood is significantly different from that observed in men.

One of these datasets has also been examined to determine if any effect of pregnancy can be discerned (45). The postmenopausal increase in lead in blood was less in those women who had ever been pregnant than in never-pregnant postmenopausal women (Fig. 4). These data suggest that prior pregnancy (and possibly lactation, although breast-feeding data were not available) had already mobilized some bone lead stores, so that less lead was available in mobilizable compartments. Anecdotal reports by a keen observer of occupational lead poisoning confirm this: in the early 1900s, Sir Thomas Oliver reported on the case of a young woman who suffered from severe lead poisoning only when she became pregnant, not while she was working in the lead industry. Oliver concluded, "I am of the opinion that not only does lead adversely affect the course of pregnancy, but that pregnancy itself may dispose to the adverse effects of lead" (46).

Lipophilic Chemicals

Another major class of chemicals that we can currently suggest may be modulated by these stages of women's lives are those stable agents, or their metabolites, that are partitioned into lipid and stored in adipose tissue. Several of the organochlorine insecticides—chlordane, lindane, dieldrin, DDT, and DDT metabolites DDD and DDE—as well as the polyhalogenated biphenyls, dibenzodioxins, and dibenzofurans fall into this category. As with the bone-seeking toxicants, adipose tissue toxicant levels in general increase with age, reflecting the long half-life and slow turnover time of compounds in this compartment.

Increases with Age and Weight Loss. Limited survey data from the U.S. National Human Adipose Tissue Survey (47) indicate that in all regions of the country, older persons have higher levels of lindane, DDT metabolites, persistent phthalates, PCBs, dioxins, and furans than do younger persons (Fig. 5). Lipophilic xenobiotics are also mobilized when body fat stores are mobilized. Studies of persons undergoing weight loss have reported rises in circulating levels of DDT and its metabolites (48, 49).

Lactation. These compounds are also mobilized into the fat that is secreted in breast milk

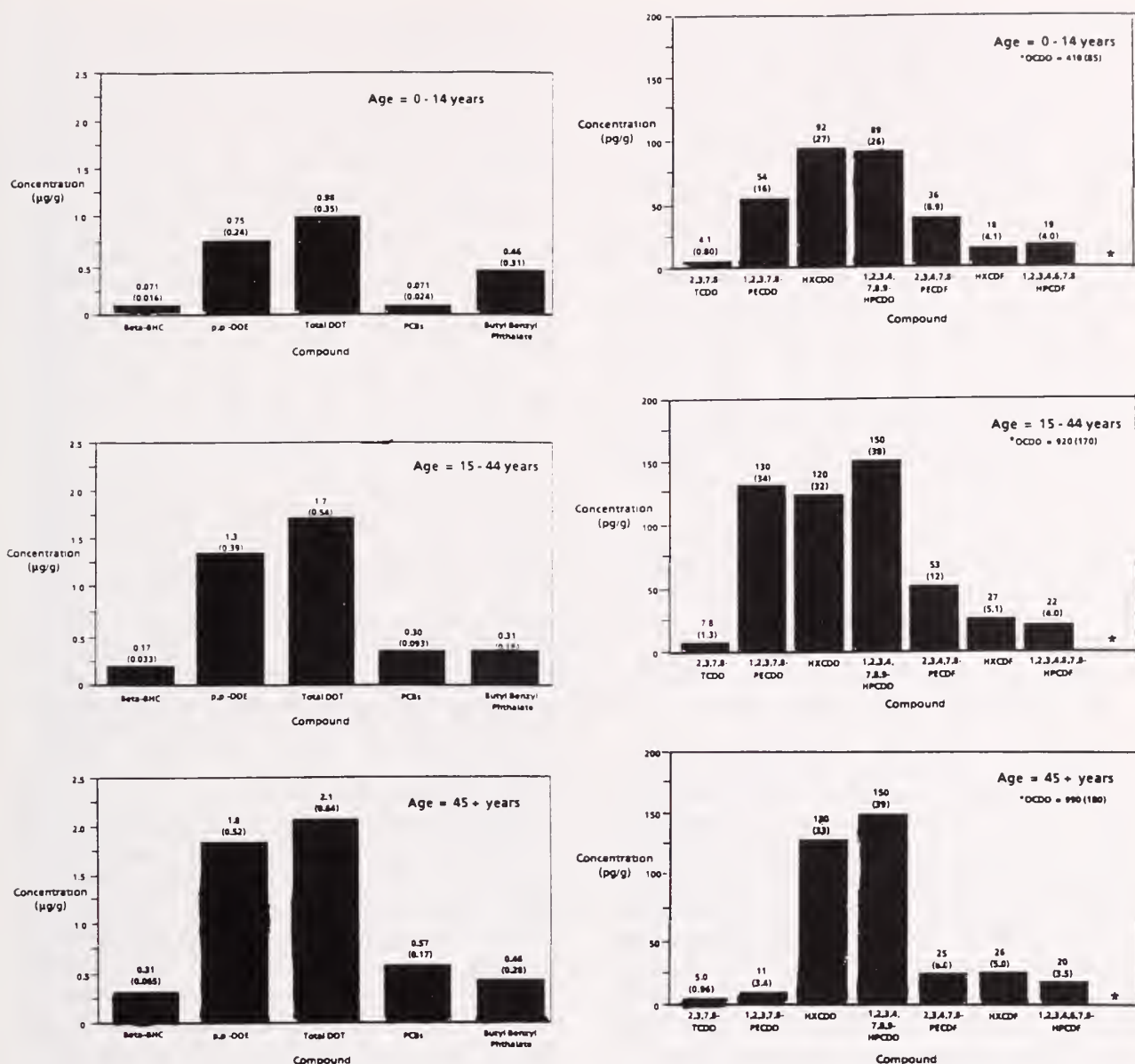


Fig. 5. Left Weighted estimates of average concentration levels of semivolatiles (wet weight, µg/g) for each age group. (Standard errors of estimates are in parentheses.) Right Weighted estimates of average concentration levels of dioxins and furans (lipid adjusted, pg/g) for each age group. (Standard errors of estimates are in parentheses.) Reprinted with permission from ref. 47.

during lactation (50, 51). These levels can fluctuate considerably (52) (Fig. 6). PCBs are primarily associated with VLDLs (53), which are preferentially utilized by breast tissue for milk triglycerides. In one study with mice, over 90% of injected tetrachlorobiphenyl was eliminated in breast milk within four days of beginning lactation, whereas after a similar injection, the body burden in nonlactating, virgin animals decreased only 20% and in animals in late pregnancy did not decrease significantly (53). Other animals also eliminate PCBs through lactation, although not as rapidly or completely (for the rabbit, see ref.

54; for the rhesus monkey, see ref. 55). The mobilization of PCBs into breast milk corresponds to an increased body burden of PCBs in nursing neonates in each of these studies. On the basis of this data, it is sometimes estimated that much of the so-called "background" level of exposure to xenobiotics such as the dioxins occurs during breastfeeding (56). But this mobilization may also have toxic consequences for the nursing mother. There are relatively few studies on this point, but some evidence suggests that circulating levels of PCBs also increase in the mother as she nurses (57). This could redistribute the chemicals to target

tissues, such as lung, liver, brain, ovary, or breast, which are vulnerable to these toxicants.

Menopause. At menopause, when fat metabolism changes, the disposition and retention of lipophiles is likely to be affected as well. It may be inferred that this change is likely to favor sequestration of lipophiles in adipose tissue, because the fat content of women's body mass generally increases after menopause. These changes in lipid metabolism may, however, affect the retention of any lipophiles to which postmenopausal women are exposed, in the diet or through other routes and pathways. Circulating levels of lipids tend to increase in women after menopause, and this may result in higher levels of some lipophiles in the circulatory compartment. Brown and colleagues at General Electric have reported that blood PCB levels are correlated with blood lipid concentrations (for review, see 58). Again, the relatively greater distribution of such chemicals into the circulation may increase the delivery of these toxicants to sensitive target organs.

Discussion and Conclusions

We have suggested that three stages of women's lives, experienced by most women, may modulate responses to toxic chemicals encountered in the environment or the workplace. Much of this modulation is related to changes in the physiology of compartments for long-term storage of persistent chemicals. Bone is a major storage compartment for many toxic metals; fat is a major storage compartment for persistent lipophiles. Although to some extent it has been assumed that these compartments are metabolic "sinks" for such toxicants, and as such represent a favorable response to exposure, we now know that in fact these compartments are in dynamic relationship with the circulation. Their retention of stored materials may change rapidly, in response to changes in exposure, compartment size, diet, or metabolic demand or alterations among the hormonal signals that control both bone and fat dynamics. With some exceptions, the three life stages—pregnancy, lactation, and menopause—tend to cause these compartments to release stored materials. The possibility that changes in the internal distribution of such toxicants might contribute to the morbidity and mortality associated with pregnancy and menopause deserves consideration.

Effects on Hypertension? One of the most obvious outcomes is the possibility that increases in circulating levels of lead may increase blood pres-

sure (59). Hypertension is an important risk during pregnancy, and the risks of hypertensive heart disease increase substantially in women after the menopause (30). The possibility that changes in the compartmentalization of lead during these physiologic stages might contribute to hypertension has not received much study.

Effects on Breast Cancer? Another possibility is that mobilization of lipophiles in adipose tissue during breast feeding might increase the exposure of breast tissue to these chemicals. This raises interesting questions about the interactions between reproductive history, breast feeding, and past chemical exposures as risk factors for such diseases as breast cancer (60).

Effects on Toxin Disposition? Many of the physiologic changes that redistribute these toxicants are hormonally driven, a fact that has interesting implications for investigating environmental toxicants that affect hormone systems, such as the so-called xenoestrogens (61). These chemicals have been hypothesized to be of special concern or risk to women because of their ability to affect reproduction and estrogen-dependent tumorigenesis. For women, the synergistic or permissive effects of these chemicals on the long-term storage and distribution of other toxicants might be equally important.

There are certainly many other ways in which sex-specific physiology could interact with toxic chemicals. First, metabolic enzymes and other functional proteins can show sexual dimorphisms. For example, there are sex differences in the gene expression and activity of the CYP450 metabolic enzymes and in superoxide dismutase activity (62, 63, 64), which might affect the rates of activation or detoxification of toxic compounds. Differences in drug:protein binding in blood serum (65) might affect the disposition of toxins within the body.

Second, functional systems in addition to those we have discussed, such as digestion and circulation, interact with the physiologic changes and the changes in hormone status of pregnancy, lactation, and menopause. For example, autoimmune diseases such as rheumatoid arthritis, Graves' disease, and systemic lupus erythematosus interact with pregnancy; symptoms are often alleviated during the period of gestation, and postpartum flare-ups are fairly common (for review, see 66). Whether these changes might modulate responses to immunotoxicants is unknown.

In addition, interactions between toxins and physiologic stage may be synergistic. For example, cadmium causes kidney damage, which leads to oversecretion of calcium. This could be impor-

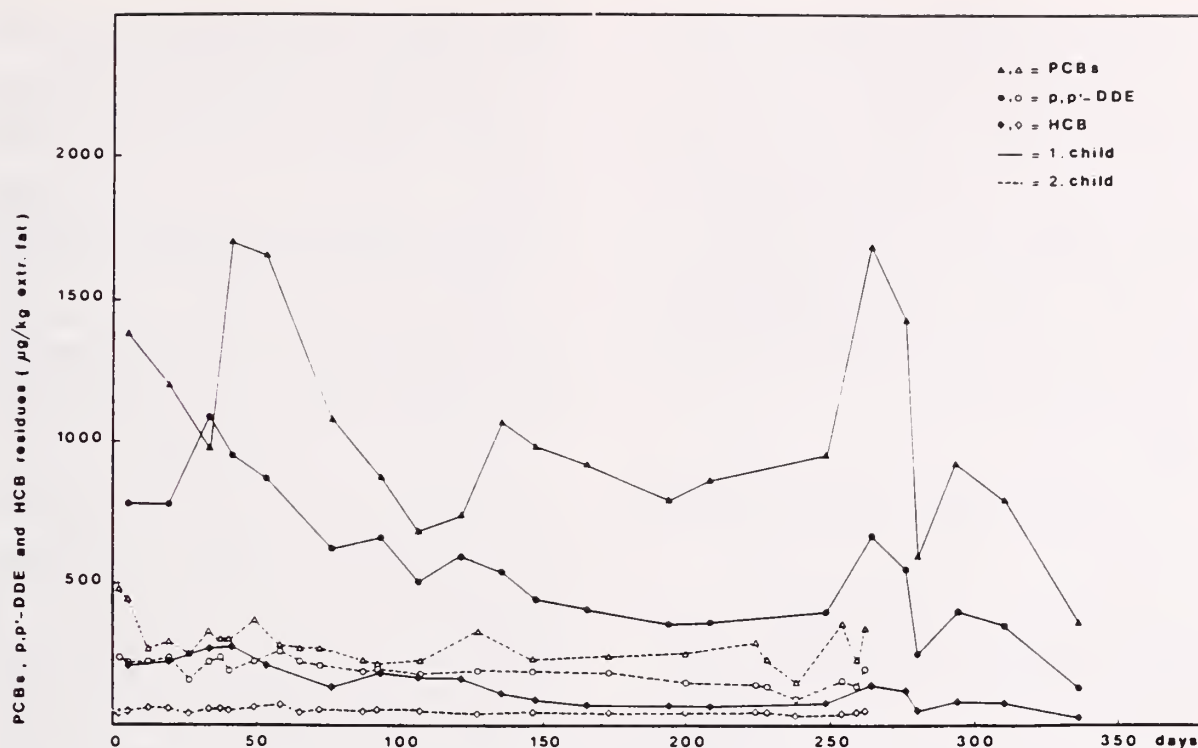


Fig. 6. Variations and differences of residue levels of PCBs, p,p'-DDE, and HCB in milk from one mother during lactation of first and second child born 3.5 years apart. Mother collected milk samples throughout the two lactation periods. Reprinted with permission from ref. 52.

tant for women of borderline status for osteoporosis, because the extra calcium loss might make the difference between disease and no disease.

Which Differences Matter? Men and women are different. Women are different from each other. Women are even different from themselves as they pass through different life stages. For toxicology, as well as many other applications of biological knowledge, the relevant question is not, Are groups of people different from each other? but rather, Which differences matter? In identifying sex-related aspects of physiology as potential modulators of toxicity, this paper begins the process of asking whether sex makes a difference; relevance must not be taken as a conclusion.

In the context of recognizing that differences exist, it is necessary to decide how to define whether a difference matters. What difference between the means of two groups would be important in looking at IQ scores, or rates of metabolic clearance? The answers might well change for different applications. We do not regulate environmental exposures based on means, so more than a divergence of means would be relevant for regulatory applications. Differences may require attention to individual parameters rather than to group statistics. For instance, a large standard deviation in metabolic rate might mean that therapeutic drug dosing needs to be based on param-

eters measured in each patient, rather than on the average.

Furthermore, if a difference of concern is identified, careful work is needed to unravel the underlying causes. As we have discussed at length, nonbiological gender factors are often closely paired with biological sex factors, so it cannot be assumed that an impact on women is mediated primarily by sex.

In this paper we have tried to investigate not how biological sex creates differences between men and women, but how biology creates differences for women. We are advocating a sophisticated understanding of physiology in basic science and toxicologic investigation. A critical eye that constantly challenges the relevance of traditional groupings is crucial to allowing science to mature without feeding prejudice and discrimination.

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Health Risk Implications of Magnetic Field Exposures

DANIEL WARTENBERG, PH.D.

Abstract

Magnetic field exposures pose serious questions to the public. The science is not sufficiently clear or consistent to result in a consensus. Some scientists view the data as strongly suggestive and argue that if the association is true, the ubiquity of exposure may be resulting in a marked underestimation of the actual risk. Others argue that the inconsistencies in the data and the specific limitations of the studies suggest that there is no association and no reason for concern. The state of the science is such that a definitive resolution is unlikely in the next few years.

In light of this uncertainty, I believe that the most prudent course of action is the prevention or limitation of exposure where feasible at limited cost and inconvenience. Be it at home or at work, prevention of exposure is simply good public health practice.

EXPOSURE TO ELECTRIC AND MAGNETIC FIELDS (EMFs) generated by transmission of electricity for residential use (so-called power frequencies) and the use of electrical appliances have emerged as major public concerns over the past two decades. First evidenced in a study of childhood leukemia in Denver, Colorado (1), several subsequent studies of residential exposures and many dozens of occupational exposure studies have provided much information from which to assess risk. Unfortunately, the picture is still very confusing. Epidemiologic studies show associations between magnetic fields and cancer far more frequently than not, but the consistent and repeatable pattern of more classical environmental hazards has not emerged. Laboratory studies of cells in culture and experimental studies of animal models do not provide corroboration of the epidemiologic data, although some anomalous results have been observed. This article briefly summarizes the results of the epidemiologic studies, speculates on some of the reasons for the observed

lack of consistency among epidemiologic studies, and makes some suggestions for the management of magnetic field exposures in occupational and nonoccupational settings.

Epidemiologic Studies

Residential Exposures. Epidemiologic studies of residential exposure to magnetic fields designed to replicate the findings of Wertheimer and Leeper (1) have focused on cancer outcomes. Some 16 studies of cancer in children have typically assessed leukemia as the primary outcome; some studies have also considered lymphoma, nervous system cancers, and total cancers (2, 3).

In general, these studies show positive associations, some of these being statistically significant. Estimates of the relative risk of exposure for subjects with cancer most often fall between 1.3 and 2.0, some ranging as high as 6.0.

The most important difference among the results of these studies is the way in which the exposure to magnetic fields was assessed. Various surrogates have been used to estimate the magnitude of the magnetic field exposure. Most assess some aspects of strength of and proximity to electric power delivery system wires (for example:

From the Department of Environmental and Community Medicine, and Environmental and Occupational Health Sciences Institute, UMDNJ-Robert Wood Johnson Medical School, 681 Frelinghuysen Road, Piscataway, NJ. Address reprint requests to the author at EOHSI, P.O. Box 1179, Piscataway, NJ 08855-1179.

linear distance; so-called wire codes, which combine linear distance with the number and thickness of wires; calculated fields, based on the historical load on the wires and the linear distance), all yielding moderately similar results. Other studies have directly measured the ambient magnetic fields in homes, either instantaneously (so-called spot measures) or over 24 hours. Results using the time-weighted average of the measured magnetic fields typically result in little or no association.

Studies of adults have been more limited. Approximately seven have been conducted, emphasizing leukemia as in the studies of children, but some also assess lymphoma, nervous system cancers, and total cancers. These studies are more equivocal, results including some weak positive and some weak negative associations.

Electric appliances represent another source of nonoccupational exposure to magnetic fields. These include clocks, microwave ovens, televisions, electric blankets, and other assorted household devices. Extensive exposure studies suggest that time-weighted average exposures from most appliances typically are small when compared with ambient magnetic fields attributable to transmission lines, in-house wiring and grounding systems (4). One exception is electric blanket use, which can result in exposures substantially higher than other sources over many hours of continuous use.

Several epidemiologic studies have assessed the association between the use of particular appliances and cancer. Results vary by studies, some show positive associations and some not. However, the paucity and low statistical power of the studies, as well as design differences among them, leave this issue even less clear than the results for studies of overall residential exposures.

Concerns also have been raised about the possible association of exposure to electric and magnetic fields and reproductive disorders. Most research has focused on exposures from video display terminals (VDTs). For that exposure, there is at best limited evidence for a weak association between VDT use and spontaneous abortion, and weaker, yet suggestive, data for association between VDT use and congenital malformations. Data on reproductive effects from other types of electric and magnetic field exposures are too sparse to be reliable.

Occupational Exposures. Following Wertheimer and Leeper's suggestion that residential electric and magnetic fields might cause cancer

(1), Milham (5) assessed the possible correspondence between occupational exposures and reported leukemia deaths, using Washington State death certificates and reported job title as the surrogate for exposure. Using a proportional mortality ratio approach, he found an association between those with "electrical occupations" and leukemia. Several studies followed, applying this same approach to other databases, and then expanding to historical cohort studies.

In general, associations were found repeatedly, particular types of occupations, notably electrical lineworker and electric engineer, showing stronger associations. Other cancers, although less well studied, have also shown elevated rates, including brain cancer, melanoma, and male breast cancer. Two recent reviews report these results in more detail (6, 7). One notable limitation is that the studies use job titles to categorize exposure, likely resulting in substantial misclassification.

Four recent studies have combined measurements of magnetic field exposures on particular job tasks with reported frequency of these job tasks by individual workers (8–11). Although the Sahl et al. study (4) showed no elevated rates of cancer, the other three showed both elevated leukemia and brain cancer. However, the reported degree of elevation of the rates of these two cancers has varied in terms of the absolute and relative magnitude of the risk. In other words, where one study showed brain cancer as the most severe risk (11), the others showed leukemia as the greatest risk (8, 10). Once again, high disease rates were detected in these studies, but the specific results lack the consistency found for other occupational hazards.

Limitations of Epidemiologic Data

As in all epidemiologic studies, these studies suffer from a variety of methodologic or design limitations. What is at issue in considering these limitations is the potential magnitude of their effects on the reported outcomes. For example, many have criticized the subject selection process of several of the residential studies. These studies used random digit dialing to select control subjects, which required the controls to be less mobile than the cases. This strategy does have an effect, but the magnitude of the effect is less than that of the exposure-cancer association observed (12).

Similarly, many have argued that confounding variables were not adjusted for adequately in

these studies. That is, other factors not included in the analyses may be the actual cause of the cancers. In fact, several confounding factors (age, socioeconomic status, traffic density) were adjusted for, either in the design (matched subject selection) or analysis (stratified or multivariate analyses), and none fully compensated for the observed associations. Although one cannot rule out confounding as a possible explanation of association in any observational study, many factors have been examined and excluded, and many more are still undergoing evaluation.

What is perhaps most perplexing about the results of the studies is the disparity in results using different types of exposure assessment (3). In particular, study results using the actual measured magnetic fields show either far less or no association than do those using surrogates. A variety of post hoc explanations have arisen, such as that the surrogates represent a more accurate long-term average exposure than instantaneous measures. Although plausible, these explanations still leave many questions unanswered. Additionally, some surrogate studies including multiple levels of exposure do not show the classic dose-response effect that one expects from most agents. Again, various explanations exist, but none is comprehensive.

Finally, everyone is exposed to magnetic fields. Be it at home, on the way to work (or shopping or school), or at work, most of us encounter substantial short-term, and possibly substantial long-term, exposures. Thus studies that compare "exposed" to "unexposed" subjects likely underestimate the magnitude of the risk, if one exists.

Recommendations for Exposure Management

Responding to concerns about magnetic fields is challenging because of the uncertainty and inconsistencies noted above. Nonetheless, given the widespread exposure, even a relatively small elevation of risk could result in a substantial number of cancers, if exposure to magnetic fields is eventually shown to be hazardous. In view of this potentially large population risk, it is good public health practice to limit exposure where limits can be achieved cheaply and without much inconvenience until we have better information on the likelihood of the hazard. Historically, scientists have failed to identify many serious hazards until the death toll was distressingly large (smoking, asbestos). Rather than waiting for enough human deaths to warrant action, good public health prac-

tice dictates prevention of exposure, when it is achievable, until the potential hazard is better understood. Although sometimes this leads to overprotection for possible risks that turn out not to be human health hazards, the cost expended in overprotection is far less than that from failing to protect from a possible risk that turns out to be real.

One complication of this strategy, however, is that the lack of consistency in study results makes it difficult to determine what aspect of exposure (peak exposure, time-weighted average exposure, time over a specific threshold of exposure) is most relevant for disease causation or prevention. Until more is known, most assume that, as with chemical carcinogens, more exposure is worse.

At home, there are a variety of things one can do to reduce exposure. We can move electrical devices such as clocks away from the bedside. We can limit the electric blankets to bed-warming, turning the blankets off prior to crawling under the covers. We can maintain a distance of a few feet between us and other appliances, such as televisions or microwave ovens, except when we need to adjust the controls or perform other functions.

Residential magnetic fields may also be due to the electric wires outside your house and the wiring inside your house. Altering these magnetic fields is more difficult and more expensive. In light of the uncertainty about disease causation, most feel that such interventions, although technologically feasible, are not currently warranted because of their expense.

Public-access facilities, such as schools, playgrounds, and libraries, are considered for magnetic field mitigation because of the number of people that use them. Technological solutions are similar to those for the home, but the cost may be spread over many more users, making it more attractive. In some instances, community residents have paid to have outdoor lines altered or put underground.

Workplace exposures are another source of concern. As in residences, so at workplaces—people spend many hours each day in the same environment. If exposure is high at either place, the time-weighted average may be high. In some instances, however, mitigation is straightforward and easy to implement. For example, exposure at the rear of VDTs is typically far higher than in the front. By rearranging the placement of desks and VDTs with this in mind, many exposures can be reduced. In other situations, the primary use of

a room or location can be altered so that rooms with high magnetic fields get limited use—as storage or file rooms, say—and those with low magnetic fields get more extensive use, as offices or meeting rooms.

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Lead Poisoning

PHILIP J. LANDRIGAN, M.D., M.Sc., ANDREW C. TODD, Ph.D., AND RICHARD P. WEDEEN, M.D.

LEAD POISONING is the most common disease of toxic environmental origin in the United States today.

Sources of Exposure to Lead

In Adults. Most adult exposure to lead occurs in the workplace by inhalation. More than 3 million workers in the United States are at risk. Industries classically associated with lead exposure include smelting, battery making, ship building, soldering, stained glass manufacture, brass foundry work, and lead-based paint abatement. More recently, construction and demolition work have become major sources of occupational lead exposure. Construction work had until 1993 been exempted from those protections. Particularly severe exposures have occurred in construction workers involved in the demolition and renovation of painted steel structures such as bridges and elevated highways (1).

In Children. Because of their normal oral exploratory behavior, children absorb most of their lead by ingestion. The mean blood lead level in children in the United States today is about 5 $\mu\text{g}/\text{dL}$, substantially lower than that of American children in the mid-1970s, reflecting enormous decreases in the use of lead in gasoline.

Lead-based paint continues to be the principal source of high-dose lead exposure for children in the United States. An estimated 57 million

housing units in the United States contain lead-based paint, and in 3.8 million homes children are intimately exposed to deteriorating lead paint (2).

Although lead-paint poisoning classically occurs among poor children living in deteriorated housing in inner cities, the disease does not respect geography or social station. Household renovations are associated with particularly severe lead exposures. Children may absorb lead from paint directly by ingesting paint chips (pica), or they may absorb it indirectly by inadvertent ingestion of lead-contaminated house dust. The latter route is the more common.

Contaminated dust and soil are pervasive sources of lead exposure for children. Concentrations of lead may reach many thousands of parts per million. In urban and suburban areas, the principal sources of lead in dust and soil are flaking paint from buildings and bridges, automotive emissions (much less now than a decade ago), and industrial releases. In general, lead in dust and soil appears to be responsible for elevations in children's blood lead levels when the lead concentration exceeds 300 to 500 ppm.

Airborne lead is generally a low-dose source of exposure for children. Automotive and industrial emissions are the major contributors to lead in air. Automotive emissions have diminished substantially since the phasedown of lead in gasoline, and industrial lead emissions have been reduced in most areas since the passage of the Clean Air Act. Although industrial emissions account for only a small fraction of airborne lead releases to the air, these stationary sources can produce concentrated zones of extremely high-dose exposure (3).

Children of leadworkers may be exposed to lead dust transported home from the workplace. In an evaluation of lead exposure among workers' children, a close correlation was found between children's blood lead levels, the severity and duration of parental exposure, and the lead concentration of household dust (4).

From the Environmental Health Science Center, Department of Community Medicine, Mount Sinai School of Medicine, New York, NY (P.J.L., A.C.T.), the Veterans Affairs Medical Center, East Orange, NJ and the Departments of Medicine and of Preventive Medicine and Community Health, University of Medicine and Dentistry of New Jersey—New Jersey Medical School (RPW). Address reprint requests to Philip J. Landrigan, M.D., M.Sc., Ethel H. Wise Professor and Chairman of the Department of Community Medicine, Professor of Pediatrics, Director of the Environmental Health Sciences Center, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1057, New York, NY 10029-6574.

Home remedies can occasionally be a source of lead poisoning in both adults and children. Numerous case reports have documented this hazard, and it appears to be especially common among ethnically isolated groups.

Background Exposure. Drinking water is a common source of lead exposure. Although lead is seldom present in drinking water in high concentrations, it contributes widely to background exposure across a wide segment of the American population. At its source, drinking water is almost always lead-free but can become contaminated as it passes through lead pipes or comes into contact with lead solder. Aggressive soft water of low pH poses the greatest hazards because it has the highest potential of leaching lead from pipes and solder.

The Body Lead Burden

The lead burden, the total amount of lead in the human body, represents the difference between the cumulative lifetime absorption of lead from all sources and total excretion. Approximately 95% of the body lead burden is stored in bone and has a biological half-life approximating twenty years (5).

In contrast, approximately 1% of the body stores are in blood (90% in red blood cells). Lead in blood has a biological half-life of only about one month. Blood, however, is conveniently accessible and is the fraction of the body burden that correlates most closely with recent environmental exposures. It is the component of the body burden most frequently measured. Thus, in the early phases of exposure to lead, the blood lead level rises rapidly and provides a sensitive indicator of recent absorption. By contrast, in persons with long-term exposure, such as workers with many years' employment in the lead industries, the blood lead level has been found to correlate poorly with current exposure; under those conditions, the blood lead level appears principally to reflect the release of lead stored in bone.

Disorders of Lead Poisoning

Intense, acute exposure to lead, either by inhalation in the workplace or by the ingestion of paint chips among children, can cause acute symptomatic poisoning. Characteristics of this life-threatening syndrome are abdominal colic, constipation, fatigue, anemia, peripheral neuropathy, and in most cases, alteration of central nervous system function. In severe cases, a full-blown acute encephalopathy with coma, convulsions, and papilledema may occur. In milder

cases, only headache or personality changes may be evident. In many instances, persons who have suffered from acute lead encephalopathy are left with permanent neurologic and behavioral sequelae.

Relatively low dose exposure to lead can cause harmful effects that are not evident on a standard clinical examination. Manifestations of lead poisoning such as anemia, neuropathy, and renal failure are evident during clinical examinations. Such covert effects as impaired biosynthesis of heme, slowed nerve conduction, and altered excretion of uric acid may not be apparent in an individual, becoming discernible only with careful epidemiologic studies.

Hematologic Toxicity. Anemia is the classic clinical manifestation of lead toxicity in the erythrocytes. The severity and prevalence of lead-induced anemia are correlated directly with the blood lead level. The anemia induced by lead may be either normochromic or hypochromic and may be associated with an increased reticulocyte count. It is caused primarily by an impairment of heme biosynthesis, but an increased rate of erythrocyte destruction may also occur. At blood lead levels as low as 10 $\mu\text{g/dL}$, lead begins to inhibit the cytoplasmic enzyme delta-aminolevulinic acid dehydratase in the heme biosynthetic pathway; the enzyme's inhibition is virtually complete at lead levels of 70 to 90 $\mu\text{g/dL}$. At blood lead levels of 15 $\mu\text{g/dL}$ in children and of 25 to 30 $\mu\text{g/dL}$ in adults, lead begins to inhibit the mitochondrial enzyme ferrochelatase, which is responsible for catalyzing the transfer of iron from ferritin to protoporphyrin to form heme (6). Ferrochelatase inhibition causes the metabolic intermediate erythrocyte protoporphyrin to accumulate to excess in erythrocytes. Erythrocyte protoporphyrin elevation is thus a measure of both lead absorption and toxicity.

Neurologic Toxicity. In the peripheral nervous system, the motor axons are the principal target of lead. Lead-induced pathologic changes in these fibers include segmental demyelination and axonal degeneration. Extensor muscle palsy with wrist and ankle drop has since the time of Hippocrates been recognized as the classic clinical sign of this toxicity.

Recent studies of the peripheral nerves in persons exposed to lead have used electrophysiologic probes to determine whether lead causes covert abnormalities in function. Slowing of ulnar nerve conduction velocity has been noted at blood lead levels as low as 30 to 40 $\mu\text{g/dL}$ (7).

Evidence for the neuropsychologic toxicity of lead at low doses has been provided by a series of

prospective studies in newborn children. In these investigations, correlations have been sought between intellectual performance in young children and lead levels in umbilical cord blood at birth. All of these studies have found subclinical but apparently irreversible decrements in central neurologic function characterized by diminished intelligence, shortened attention span, and slowed reaction time (8).

Renal Toxicity. The effect of inorganic lead on the kidneys depends on the rate of absorption, the quantity absorbed, and the time at which diagnostic tests are performed. Excessive lead absorption is associated with four conditions affecting the kidneys: hypertension, chronic tubulointerstitial nephritis, the Fanconi syndrome, and saturnine gout. Kidney disease has not been decreased as resulting from exposure to organolead compounds such as the gasoline additive tetraethyl lead, although many petroleum derivatives, including a wide variety of industrial solvents, can induce tubular cell injury.

Hypertension: Continuous low-level absorption of lead from the general environment modulates blood pressure even when both blood lead and blood pressure are within accepted normal ranges. The Second National Health and Nutrition Examination Survey (NHANES II), performed between 1976 and 1980, included blood lead and blood pressure measurements of almost 10,000 Americans. Analysis of these data showed that blood lead predicts blood pressure in the general population (9).

Higher levels of lead absorption are associated with hypertension and renal disease. The CaNa_2EDTA lead-mobilization test has been used to suggest a role for lead as a cause, or contributing cause, in some patients believed to have "essential hypertension with nephrosclerosis" (10). The lead-mobilization test may demonstrate the presence of excessive lead stores when current blood lead measurements are within the range considered acceptable in the occupational setting ($<40 \mu\text{g/dL}$). The latent period between exposure and disease is often measured in decades; hypertensive cardiovascular-renal disease is not evident for 3 to 30 years after initial exposure. The duration of hypertension is usually shorter in patients with elevated lead stores than in hypertensives without excessive lead but with comparable reductions in the glomerular filtration rate. Lead may also contribute to the disproportionate number of African-Americans with end-stage renal disease attributed to hypertensive nephrosclerosis and diabetic nephropathy.

The mechanism whereby lead absorption

causes hypertension is by no means clear, but increased intracellular vascular smooth muscle calcium has been suggested as a possible mediating factor (11).

Tubulointerstitial nephritis: Moderately high levels of lead absorption occurring over many years may cause tubulointerstitial nephritis (TIN) and renal failure with or without hypertension and saturnine (lead-induced) gout. In chronic lead nephropathy, renal biopsies show nonspecific tubular atrophy and interstitial fibrosis with minimal inflammatory response. Arteriol changes indistinguishable from hypertensive nephrosclerosis are found, often in the absence of clinical hypertension. Intranuclear inclusion bodies, characteristic of acute lead poisoning, are often absent in chronic lead nephropathy.

Proteinuria is initially minimal or absent. In contrast to cadmium nephropathy, urinary excretion of low molecular weight proteins and renal tubular cell enzymes is not remarkable in the absence of renal failure. Nevertheless, excretion of N-acetyl- β -D-glucosaminidase (NAG), a lysosomal enzyme, has sometimes been reported to be greater among lead exposed workers than among non-exposed employees, a non-specific finding (12).

The Fanconi syndrome: Acute lead poisoning, such as that encountered in children with pica and in experimental animals that have undergone massive lead absorption over a few weeks, is characterized by a transient proximal tubule reabsorptive defect (Fanconi syndrome), and lead-containing intranuclear inclusion bodies in proximal tubule cells, superimposed on the classical symptoms of acute toxicity. The Fanconi syndrome occurs in children with encephalopathy in whom blood leads usually exceed $150 \mu\text{g/dL}$. The tubular transport defect is rapidly reversed by chelation therapy administered to treat the far more dangerous encephalopathy. Acute lead poisoning may also produce prerenal azotemia, presumably mediated by salt wasting, volume depletion, and renovascular spasm.

Saturnine gout: Continuous high-level exposure to lead has been recognized as a cause of TIN in gout (saturnine gout) since 1862 (13). Hyperuricemia and gout are common among individuals who have undergone excessive lead absorption, apparently the result of decreased excretion and increased production of uric acid. Although hyperuricemia invariably accompanies renal failure, gout is rare in patients with renal failure except in patients with lead nephropathy. On the other hand, half of uremic patients with lead nephropathy have clinical gout.

Reproductive Toxicity. A body of experimental evidence indicates that lead at high doses is toxic to reproductive function in both male and female laboratory animals. Clinical reports, most of them from the first half of this century, have also described reproductive toxicity in workers of both sexes subjected to high-dose exposures to lead; the incidence of spontaneous abortion was reported to be higher in female lead workers and in the wives of male lead workers than in other populations.

In male workers who have been heavily exposed to lead (mean blood lead level, 74.5 $\mu\text{g/dL}$) and also in men with moderately increased lead absorption (mean blood lead level, 52.8 $\mu\text{g/dL}$), decreased sperm counts and an increased prevalence of morphologically abnormal sperm have been reported (14).

Noninvasive X-Ray Fluorescence: Measurement of Lead in Bone

A newly applied technology that holds promise for the accurate, noninvasive assessment of long-term lead exposure is the measurement of bone lead concentration by x-ray fluorescence (XRF) analysis (15–17). This technique offers a relatively rapid approach to the individual assessment of body lead burdens. It takes advantage of the fact that the half-life of lead in bone is several decades. Moreover, the radiation dose is minimal, amounting to only about 0.2% of the radiation delivered by dental x-ray studies.

X-ray fluorescence analysis may be undertaken using either K or L x-rays, and instruments of both types have been developed. The K instrument has several intrinsic advantages over the L instrument.

First, the K instrument samples lead across the entire transverse section of bone, in contrast to the L instrument, which obtains 90% of its signal from only the most superficial 2 mm. If there is variation in the concentration of lead across the bone, the L measurement will fall victim to this variation, but the K will not.

Second, the K instrument does not require a measurement of the thickness of the overlying skin, whereas the L instrument is sensitive to any error in the required measurement of skin thickness.

Third, the K instrument is relatively insensitive to movement of the subject during the sampling period, whereas the L instrument is very sensitive to movement; given a sampling time of about 15–30 minutes, this consideration is not trivial.

Fourth, the L x-ray fluorescence instrument has not been well validated. However, there may be detailed modeling studies in which it would be desirable to examine lead content simultaneously in several bone compartments. In such circumstances, the combined use of the K and L instruments might offer uniquely valuable information on the kinetics of lead.

In vivo tibial K-XRF has been used for clinical evaluation of bone lead stores in patients whose lead absorption is suspected to have been excessive (18). Serial measurements have shown the reduction of bone lead occurring over years in the absence of continued exposure and more rapidly during chelation therapy. Sustained high levels of bone lead following chelation therapy have indicated persisting elevated lead stores from prior pica. In a patient with renal failure, XRF demonstrated massive lead stores when chelation testing was not possible. In other cases, bone levels have indicated the possible contribution of lead nephropathy to renal diseases of nonlead etiology. In individuals exposed to lead during home renovations, XRF has provided reassurance that past exposure did not result in elevated body lead stores decades later. In the occupational setting, XRF has documented the magnitude of cumulative lead stores in workers whose exposures varied in intensity and duration.

As in vivo tibial XRF becomes more generally available, its safety, specificity, and simplicity should make it an important alternative to cumbersome chelation tests and potentially misleading blood lead measurements.

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Incineration:

Health and Environmental Consequences

MICHAEL GOCHFELD, M.D., PH.D.

Abstract

Incineration is considered one of the four primary ways to manage solid wastes, in conjunction with source reduction and reuse, recycling-composting, and landfilling. Incineration is currently used to destroy household and institutional solid waste, hazardous chemical waste, and medical and biological waste by reducing volume and destroying some harmful constituents. The process of incineration induces chemical changes that may produce harmful products that can escape through the stack, causing air pollution, or that can remain in the bottom ash, eventually finding a way into landfills. Although sound engineering design and operation can theoretically eliminate most harmful pollutants, strong institutional controls are required to assure that incinerators are maintained and operated according to specifications. Incineration is often viewed as a "cop-out," avoiding the socioeconomically complex changes required to reduce the generation of solid waste. Incineration should be incorporated on a limited basis into a context of comprehensive approaches to source reduction, recycling, and reuse.

SOLID WASTE is becoming a literally mountainous problem (1). By 1980, Americans were disposing of an estimated 3.5 kg/person per day (2), nearly double the amount in 1960. The United States is the largest producer of waste and suffers severe cost consequences (3) as well as potential health problems (4). New York City alone estimates about 14 million metric tons of solid waste per year (5).

The management of solid waste, particularly the role of incineration, is a subject of heated (the play on words is intended) debate (2, 4, 6). Environmentalists argue for a Three R's solution: source reduction, reuse, and recycling. Any other solution, whether permanent or temporary, is viewed as thwarting the definitive solution (7). Solid waste managers, for example the New York City Department of Sanitation, seek a multimedia approach, in which, surprisingly, incineration plays an increasingly important role (5). In this

paper I examine the health-related issues surrounding incineration in the context of the greater social challenge of waste disposal. Indeed, the health implications of waste management are not easily separated from the political and economic aspects (2, 6, 7, 8).

The health impact of various waste management approaches can be considered under five categories:

- direct exposure to hazardous substances emitted to the air
- indirect exposure as toxic air pollutants reach surface or ground water, or contaminate soil and enter food chains
- the impact of odor, noise, traffic, aesthetics
- impact on sanitation and waste management workers
- redirection of financial resources from one social need to another

Although hazardous waste is regulated and managed separately, some hazardous waste does enter the solid waste system. However, the greatest health concerns from waste management surround incineration which, under certain circum-

From the UMDNJ-Robert Wood Johnson Medical School and Environmental and Occupational Health Sciences Institute Piscataway, NJ. Address reprint requests to the author at the Environmental and Occupational Health Sciences Institute, 681 Frelinghuysen Road, Piscataway, NJ 08855-1179.

TABLE 1
Components of a Waste Management System

Source reduction
Social changes in product use/packaging
Reuse
Recycling/composting
Source separation
Separate collection
Transfer stations and drop-off facilities
Material recovery facilities (with or without incineration)
Composting
Incineration
Waste-to-energy
Resource recovery
Cogeneration
Landfilling
Raw garbage
Durable goods
Bottom ash
Special solid waste processing
Medical waste
Harbor debris
Sewage sludge

TABLE 2
Estimated Composition by Weight of Solid Waste Generated in New York City

Type of Waste	%
Municipal solid (residential, institutional, commercial, industrial)	55-60%
Construction and demolition* (including hazardous materials such as asbestos)	15-20%*
Dredge spoil (for a coastal city with a harbor)	15-20%
Sewage sludge	1-2%
Medical (including potentially infectious material)	1-2%*
Harbor debris	<1%
Agricultural	<1%
Mining (negligible in New York)	

* Hazardous waste not included in solid waste.
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stances, can form highly toxic chemicals, such as dioxins (7, 9), and which leaves behind an ash residue rich in toxic metals.

Although most of us see the garbage stream beginning at the wastebasket and ending with the early morning clang as garbage cans or dumpsters are emptied into trucks, there are actually many ways to collect garbage and many ways to process it (1, 5). These can be combined in various systems and on various scales to serve populations of varying size and density (2, 5, 8). Landfills, formerly called garbage dumps or, in En-

gland, rubbish tips, have long been the mainstay of solid waste management. But in many states, landfilling is being phased out or severely limited, hauling and tipping fees are increasing, and municipalities and counties are required to develop acceptable alternatives, which usually involve multiple approaches (Table 1).

The solid-waste stream begins in homes, businesses, and institutions. Construction debris and harbor debris join it legally; hazardous chemical waste, biohazardous medical waste, and high and low level radioactive waste do not join the same stream, but are regulated and managed separately. The combined waste stream includes materials that can be reused as is or can be recycled into a different form, and also includes waste that is combustible, putrescible, or neither (old appliances, furniture) (5).

The urgency of managing this massive flow regularly can be seen in circumstances of labor disputes where garbage pickups are halted for more than a week, resulting in an accumulation of putrescent waste on city streets. Moreover, household garbage is only a small component, the tip of the iceberg, of solid waste (Tables 2, 3, 4) (5).

Waste Streams

Municipal Solid Waste. Municipal solid waste varies in composition, by source, from place to place, and even by day of week or month of year (Table 3). Airborne emissions can arise at the generation site, during collection, transportation, and tipping, and during various stages of treatment.

Municipal solid waste has three components: residential, commercial, and institutional. Residential waste, the familiar "garbage," is a mixture of food scraps, packaging, newspapers, and unwanted household items, both disposable and durable (1).

Commercial waste contains, in addition, much office waste, such as paper, manufacturing waste, and large amounts of packaging, such as corrugated cardboard.

Institutional waste comes from hospitals, schools, and other institutions which produce large quantities of waste from a single source. Potentially infectious biohazardous or medical waste must be separated from the other components. There can be an economy of scale in dealing with large institutions. A cost incentive-disincentive scheme may encourage institutions to purchase materials and use them in a way that minimizes waste (source reduction).

Construction and Demolition Waste. Waste from construction and demolition includes a wide variety of material often saturated with paints or preservatives, and sometimes includes asbestos. This is bulky material which may have low BTU content and be difficult to incinerate. Contractors are legally required to separate hazardous materials such as asbestos and remove them from the solid waste stream to a separate hazardous waste stream (5).

Sewage Sludge. Sewage can be treated by chlorination, aeration, and dewatering. After dewatering, the dry treated sludge is usually non-infectious, but residual contaminants include metals and organics. Such sludge can no longer be dumped at sea (although legislation to reverse that is pending in Congress), and various land-based uses are being considered. Sludge can be composted for agricultural uses, but potential mobilization of the toxic metals it contains poses a challenge, and will probably restrict it to nonfood crops (flowers, lawns) (10).

Medical Waste. Many disposable materials routinely used in clinical practice can be replaced by reusable ones (returning to practices before the 1960s). The infectious potential can usually be inactivated locally by autoclaving or chemical treatment, but today most of this waste is simply red-bagged and transported to distant incinerators that specialize in biohazardous or infectious waste. Much of the material that goes into red bags is noninfectious and inappropriate, but there is no institutional mechanism for separating it. Since much of this waste is plastic, medical waste incinerators must be designed to eliminate emissions of hydrogen chloride and phosgene, to avoid formation of chlorinated aromatic compounds such as dioxins (7).

Harbor Debris. Most of us never see this poorly studied waste stream, which is mainly waterlogged wood, often saturated with toxic preservatives such as arsenic, pentachlorophenol, or creosote. Various other noncombustible harbor components include cement and scrap metal. Incineration plays little role in this waste stream, much of which could be reused or recycled, if there were an economic incentive. This stream is not inconsequential in port cities such as New York (Table 1).

Dredge Spoil. The U.S. Army Corps of Engineers, charged with maintaining the navigability of coastal and interior waterways, conducts periodic dredging to reestablish deepwater channels for shipping. The sediments of a harbor are often extensively contaminated with heavy metals and polyaromatic hydrocarbons, and dredging some-

TABLE 3
Composition of a Residential Waste Stream for New York City[‡]

Component	%
Food waste	11%
Plastic bags	5%
Magazines/glossy	4%
Textiles	4%
Grass & leaves	3%*
Glass containers	3%
Bulk items	10%
Newsprint	9%
Miscellaneous organic matter	7%
Corrugated papers	6%
Aluminum cans	0.5% [†]
Poisons	0.02%
Batteries	0.06%
Medical Waste	0.02%
Pesticides	0.01%

* About 30% nationwide (much higher in nonurban areas).

[†] About 1% nationwide.

[‡] About 30% is loosely definable as "packaging."

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TABLE 4
Profile of a Typical Solid Waste Day in New York City

	Tons	
	Subtotal	Total
Municipal solid waste		12,500*
Recycled paper, glass, metal	300	
Incinerated	1,200	
Landfilled (mainly Fresh Kills)	11,000	
Private solid waste		14,000
Recycled	2,500	
Landfilled (outside city)	11,500	
Harbor dredge debris		
Dumped at sea		8,700
Floatable Harbor debris		
Burned on barges at sea		100
Construction/demolition debris		
Unknown outcome		8,300
{shredded for recycling; landfilled}		
Dewatered sewage sludge		
Dumped at sea		700
Red-bag medical waste		
Incinerated		200
TOTAL		43,350 tons

* Residential and institutional waste only; commercial, corporate, and industrial wastes are collected and disposed of by private haulers.

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times meets substantial local opposition (for example, recent controversies over dredging in New York Harbor). The U.S. Environmental Protection Agency has designated offshore sites where this material can be dumped. However, the pos-

sible resuspension of contaminated sediment in water at the source, and the ultimate security of the ocean dump sites, make ocean dumps highly controversial, and alternative approaches to managing dredge material are being sought.

Agricultural Waste. Animal waste from stockyards, vegetation waste after harvesting, container waste (empty bags and cans), and unused pesticides are serious problems. As an example, water pollution from duck farms on Long Island has been a major environmental concern.

Mining Waste. Mineral matter such as slag and construction debris is included in mining waste. Such waste does not usually enter the municipal waste stream but is a major source of water pollution. The growth in developing nations of small-scale gold-mining and extraction by amalgamation is greatly increasing the global use of and contamination by mercury (11).

Hazardous Waste. Hazardous waste sometimes becomes a component of solid waste streams, but it is managed separately.

Solid Waste Management

A waste management system (Table 1) embodies waste prevention (including source reduction, reuse, and recycling) and waste treatment (including incineration or waste-to-energy conversion, composting, landfilling, and various modifications of these). The plan should consider environmental impacts on (a) air quality, (b) water quality, (c) traffic, (d) noise, (e) odor, (f) socioeconomic effects, and (g) community acceptance.

Solid waste managers are faced by huge volumes of paper products, cardboard boxes, textiles, plastic, food and other organic waste, and metals and glass. The major management options are reuse and recycling, incineration, composting, and landfilling, with many modifications of these basic themes. Table 4 shows a typical day for New York City's waste managers, excluding waste collected by private haulers from commercial sources (5).

It is easiest to visualize the solid waste management system as a three-dimensional matrix: 6–8 waste streams (Table 2) handled by various approaches (Table 1), each combination of waste technology producing various environmental impacts, both adverse and beneficial to air, water, soil, food, and human health. Each combination of technologies can be treated as a complete scenario. The hazards associated with each scenario include transportation accidents, occupational injuries, air pollution, water pollution, aesthetics, and economics.

Source Reduction. Ultimately source reduction must be the mainstay of solid waste management. Intelligent consumers, both private and commercial, must purchase and use materials that minimize waste. Consumer education programs already play a large role in reducing waste, particularly in conjunction with community recycling programs. Incentives for source reduction should encourage replacement of disposables with reusable supplies and equipment (2), and should discourage wasteful packaging, which now comprises a major component by volume of the municipal waste stream. However, commercial interests that produce such disposable materials and packaging oppose source reduction, and, in a surprise move, the New Jersey Assembly recently redefined "source reduction" to mean "emission control."

Reuse. Many containers and goods can be reused or the useful life prolonged. Many items, such as photographic, electronic, and computer equipment, have been converted from the durable to the nondurable category, since they are rapidly replaced by improved technologies, or the costs of repairing them approach the costs of purchasing state-of-the-art replacements. Much of this waste is bulky, and disposal is costly. Designing such items to facilitate repair or reuse of components (for example, the computer chassis) would greatly reduce waste. Reduction of use of disposable items may depend on financial disincentives which build the cost of disposal into the purchase price.

Recycling. Many common materials—metal, glass, plastics, paper, textiles—and bulky items such as appliances are recyclable, and these account for nearly half of municipal solid waste (1). A successful recycling program has three essential components:

- recyclable waste must be separated at some point (source, transfer station, or incinerator)
- technology must be available to convert this waste to a usable alternative product
- there must be a market for the new product, which must be available at a competitive price or must be subsidized.

The sluggishness of recycling is due in part to the fact that virgin materials may be less costly than recycled ones. Contrary to popular belief, the public readily accepts and participates in source separation and recycling. The elimination of the deposit bottle in the 1950s came through lobbying by the glass container industry, not the general public.

Industries will not develop a cost-effective means of recycling a material until there is a sure

supply of that material, and communities may not recycle that material until there is a demand. In this case the supply can drive the demand, as well as vice versa.

How Incinerators Work

Although people may have burned garbage for many years, the first municipal solid waste incinerator was built in Leeds, England, in 1874, to destroy waste matter associated with an epidemic of cholera. In 1884 the first United States incinerator was built on Governor's Island, N.Y., and in 1904 an incinerator was producing enough heat to generate enough electricity to light the Williamsburg Bridge. The concept of waste-to-energy facilities was slow in taking root in the United States for two reasons. The electric utilities were not interested in purchasing or transmitting the power so produced (5), and the environmental community saw this as a ploy to continue incinerating in lieu of recycling.

Solid waste management can be viewed as competition between its four primary components. Whereas landfilling was formerly the only and is still the dominant approach, incineration has increased to account for at least 10% of certain streams, and a much higher percentage is projected for the future (5).

Many solid waste management systems incorporate incineration as a component for reducing the volume of waste and eliminating certain toxic or infectious components (5, 6). In addition to reducing the volume of many materials (wood, paper, plastic), combustion is a complex process involving high-temperature oxidation, during which many chemical reactions can occur. The incomplete combustion or pyrolysis of wood, for example, produces a wide array of organic molecules, including lignin. The pyrolysis of plastics releases cyanide (from nitrites) and chlorine (for example from polyvinyl chloride plastics). These highly toxic constituents are also highly reactive with other organics to produce new toxic and irritant substances.

The effectiveness of incineration is influenced by several factors, both social and engineering. Despite the wide variety of incinerators, they contain three structural components: feeder, burner, and stack (with pollution control devices).

Feeder. The nature and quality of the material to be burned (the so-called "feed stock") is crucial (5, 6). This feed stock is delivered (usually by truck) and, in communities with poor source separation, the "feed" must be presorted in some

way (manually, mechanically, or both) to remove recyclable and noncombustible components.

Burner. The remaining feed stock is transferred to a burner. Although major technological developments have gone into the design of the burner, the three paramount considerations are the temperature achieved, the residence time (how long the waste remains in the burner), and the mixing with oxygen. Incomplete mixing results in incomplete combustion. Temperatures over 1400° can completely destroy most organic matter and oxidize many metal salts, but higher temperatures are required to destroy certain toxic compounds, such as polychlorinated biphenyls (PCB's) and dioxins.

Depending on the feed stock, the main pyrolysis products include carbon monoxide, nitrogen dioxide, sulfur dioxide, cyanide, hydrogen chloride, phosgene, acrolein, formaldehyde, other aldehydes and organic acids, benzene, chlorine and chlorinated hydrocarbons, ammonia, and nonvolatile substances such as phenol, phthalates (from plastic), dioxins, and furans. Potentially toxic metal salts are destroyed, but the elements themselves remain, usually in the bottom ash on the floor of the burner. This ash, often highly toxic, must be removed to landfills.

Stack. After the burn, the hot gaseous material (flue gas) remaining in the burner passes to the stack, where it escapes to the atmosphere after traversing a train of pollution control devices (PCDs) that remove both particulate and volatile constituents. The material emitted to the air contains a gaseous phase and a solid aerosol of fine particulates (soot and smoke). The flue gas is hot and gaseous and under ideal conditions, contains carbon, carbon dioxide, and water vapor. However, in reality it will also contain carbon monoxide and other incomplete combustion products (including some listed above). Significant chemical reactions can occur in the stack and even in the atmosphere while gases are still heated. Air pollution modelers estimate how such gases dissipate in the atmosphere and how they may be transported to human "receptor" or "target" populations (12). The fate and transport of contaminants in the flue gas are influenced by whether the material is in vapor, liquid, or solid phase, and on the stack velocity and height. Exposure assessment calculations are mainly for the inhalation route, but ingestion and occasionally even dermal absorption contribute significantly to exposure (6, 9, 12).

Unfortunately, there is remarkably little data collection on incinerator emissions. A few controlled burns have been performed (13–16),

and many unsystematic air measurements and a small number of studies have been made at fires (17, 18).

Issues in Incineration

Incineration takes place in the context of an array of waste management options.

The regulatory climate has affected the options available for managing waste. Ocean dumping of sewage sludge has been phased out, most medical waste incinerators have been closed, the burning of harbor debris (including huge creosote-treated beams) is being phased out. Individual municipalities and states may have their own waste management regulations, among which recycling ordinances are increasingly common. For example, New York City's Solid Waste Management Act and its implementing regulations (19) require that the city (a) prevent wastes at the source, (b) reuse, recycle, or compost as much as possible, (c) recover energy, and (d) landfill only material not amenable to other strategies.

Case Study: Solid Waste in New York City.

On a typical day, New York City's 7.5 million residents and 1.5 million visitors produce more than 40 thousand tons of waste (Table 4). Some of this is recycled, some is burned, and some is landfilled, both within and outside the city. New York City operates the world's largest landfill at Fresh Kills on Staten Island. The various wastes are collected at the source, transported by truck and barge, and then treated. These procedures require costly labor and generate odors, noise, and a visual impact, as well as contributing to traffic congestion and, to some extent, to air pollution. A cost estimate of \$5 million per day is conservative.

In 1988 New York City passed the Waste Management Act (5), which targeted 10% waste prevention and 40% recycling by 1997, and in 1989 a law required 25% recycling by 1994, a target not yet met. Many incinerators, including those in apartment buildings, were closed in the 1970s to prevent air pollution, and many inadequate medical facility incinerators were closed by 1992, to conform to the city's *Guidelines for the Control of Toxic Ambient Air Contaminants* (19).

In the 19th century, New York City made use of its garbage in land reclamation, filling in canals (Canal Street), salt marshes (western Houston Street), and ponds (areas of lower Manhattan). Odors and the threat of disease discouraged this form of landfilling by the end of the 19th century (5). The city reached out to vacant land on its periphery, and dozens of landfills were used

until these too became surrounded by residential communities and were closed.

Incineration of combustible material has remained a major part of the solid waste management system (20, 21), and is an important part of the New York City Department of Sanitation's comprehensive solid waste management plan. This plan, publicized in 1992 (5), includes three components: (a) an integrated system of prevention strategies, collection-transportation-processing and disposal facilities, (b) monitoring programs to influence future policy decisions, and (c) pilot-scale research and development facilities to develop and test new waste management options.

For example, for its long-term comprehensive waste management program, New York City planned on composting 7% to 14% and recycling 20%–30% of its waste stream, relying on up to 60% for incineration (or waste-to-energy) facilities. A minimum of 15% of waste (including incinerator ash) required landfilling.

Risk and Incineration

Incineration is embodied in facilities that include the recovery of heat for various purposes as well as facilities for resource recovery (20, 21).

Data Limitation. That health risks associated with incinerator emissions have become highly controversial is partly due to the absence of sound data (2, 4, 6, 22). Scientific studies of the "cooking" of garbage are not readily funded, while firms that construct and market incinerators seldom obtain systematic data and rarely make their data publicly available, if they did, assertions about specifications could be critically appraised. Indeed, the first example of a balanced design for studying emissions under varied operating conditions showed that in 1 out of 4 runs, the operating conditions were not met (22).

A serious limitation of data that do exist is that most available reports on pollutants released from waste treatment facilities list only the mean values, giving little information on the variability or range of the data. Exposure assessors would need the upper 95% confidence limit or variance to make sense of such data. Actual exposures may be expected to exceed the mean nearly half the time. Similarly, many measurements are made between the burner and the stack, and do not reflect the true emissions, which can differ significantly (16, 22, 23).

Toxic Agents Not Used in Risk Assessments. Many of the hazardous substances potentially emitted from an incinerator are carcinogens. But others have organ toxicity for which the Environ-

mental Protection Agency has been able to estimate a reference dose (maximum daily allowable intake). The national ambient air quality standards include primary and secondary standards for six criteria pollutants (Table 5) established under the Clean Air Act. Many states have in turn adopted or modified these as state standards or guidelines (19). The ratio of projected emissions or resulting air concentrations to an existing standard or guidelines is called a hazard index. Its reciprocal is called a protection index. A hazard index of greater than 1 is unacceptable and requires active intervention to reduce exposure, but one should remember that the reference dose itself has built-in safety factors (6). Of all the hazardous materials potentially emitted from incinerators, dioxins have been the main focus of public concern, but dioxins are not necessarily the most significant agents from a public health perspective. Several of the more hazardous and common combustion products are discussed briefly below.

Carbon monoxide (CO) is always present in incineration, but efficient mixing and oxygenation reduces the amount emitted. Acute exposures causing dizziness, headache, nausea, weakness and tachypnea, followed at higher doses by loss of consciousness, coma, convulsions and death are not relevant to evaluating incinerators. Chronic exposure to elevated CO levels is a minor part of risk assessments for incineration.

Oxides of nitrogen (NO): Nitrogen dioxide, nitrous oxide, and other oxides of nitrogen are released on combustion of organic compounds, many of which contain nitrogen (amines, amides, heterocyclics). Nitrogen dioxide, the most serious offender, is irritating to the eyes and throat, and can yield nitric acid when dissolved in the liquid on the mucous membranes. These and other acid gases account for some of the respiratory damage in firefighters (24, 25).

Hydrogen chloride (HCl): With the dramatic increase in the use of polyvinyl chloride materials, more chlorine is available for high-temperature reactions with hydrogen or organics in combustion. This is a highly irritating compound, but chronic exposure is not considered in risk assessments.

Hydrogen cyanide (HCN): Incineration of wool, nylon, acrylonitrile, urethane, and other plastics which contain urethane cross-linkages may yield hydrogen cyanide. Exposure and illness from burning acrylonitrile have been documented for several major fires. Sublethal exposure to cyanide may produce a variety of symptoms—weakness, headache, nausea, vomit-

TABLE 5
Primary and Secondary National Ambient Air Quality Standards (NAAQS), New York State Standards, and Related Criteria

	Primary NAAQS	Secondary NAAQS	NY State Standards 6 NYCRR Pt 237
CO			
8 hr ave	9 ppm	9 ppm	9 ppm
1 hr ave	35 ppm	35 ppm	35 ppm
SO₂			
1 yr	80 µg/m ³ *		.03 ppm
24 hr	365 µg/m ³ †		.14 ppm
3 hr		1300 µg/m ³	.50 ppm
NO₂			
1 yr	100 µg/cu	100 µg/m ³	.05 ppm
Ozone			
1 hr	235 µg/m ³	235 µg/m ³	.08 ppm
PM-10			
1 yr	50 µg/m ³	50 µg/m ³	NA
24 hr	150 µg/m ³	150 µg/m ³	NA
Pb			
3 mo	1.5 µg/m ³	1.5 µg/m ³	NA
TSP			
1 yr			75 µg/m ³
24 hr			250 µg/m ³
Settleable particulates			
30 day			6 mg/cm ² /mo
Hydrocarbons (excluding methane)			
3 hr			.24 ppm
Beryllium			
1 mo			.01 µg/m ³
H₂S			
1 hr			1 ppm

NA, not available.

* .03 ppm standard temperature and pressure (STP).

† .14 ppm STP.

ing, confusion, and other symptoms of central nervous system toxicity, including coma. However, this chemical is usually not considered in risk assessments.

Benzene: At high concentrations, benzene is a central nervous system depressant, but incinerators emit low concentrations of this leukemogen. A New Jersey Department of Health study found that benzene was present in most fires, and often at levels exceeding 1 ppm (18). However, the contribution from incinerator emissions is usually low.

Formaldehyde (HCHO): Many materials contain formaldehyde or substances that form formaldehyde on combustion, including phenolic resins present in plywood and laminates. Formaldehyde, a colorless gas, has a characteristic odor and is highly irritating to eyes and mucous

membranes. Individuals vary greatly in sensitivity to formaldehyde.

Phosgene (COCl_2): Phosgene is a highly reactive compound widely used as an industrial raw material and is well known as a chemical warfare agent. It is commonly released from incineration of plastics and may be emitted if there is incomplete mixing in the burner. It is odorless and is not immediately irritating; it can therefore reach the lower respiratory tract, where it dissociates, releasing HCl and causing pulmonary edema.

Acrolein ($\text{HCH}=\text{CHCHO}$): Combustion of propylene, a common plastic, releases acrolein, which is severely irritating to eyes and respiratory tract even at concentrations as low as 0.25 ppm. The OSHA PEL is 0.1 ppm. Acrolein was found in 69% of fire atmosphere samples (17).

Toxic Agents Used in Risk Assessments. The following are the substances usually considered in risk assessments for incineration.

Polychlorinated biphenyls: Although production and most uses of PCBs were terminated prior to 1980, these persistent chlorinated hydrocarbons were widely used, particularly in electrical equipment, and are still present in old transformers and capacitors as well as in plastic materials. If not removed from the waste stream, these materials can be emitted. The high temperatures required to destroy PCBs may not be met in a standard solid waste incinerator.

Chlorinated dioxins and furans (PCDD, PCDF): The polychlorinated dibenzodioxins and furans are usually the "drivers" in risk assessments for incineration. They can be formed by the combustion of wood or paper, yielding the phenolic compound lignin, and plastics, releasing chlorine. Although most environmental health concerns have focused on the most highly toxic dioxin (2,3,7,8 tetrachloro dibenzo-p-dioxin), combustion produces many of the less toxic, higher-chlorinated compounds, the hepta and octa chloro compounds (9, 16, 23); however, an average of 34 $\mu\text{g/hr}$ of 2,3,7,8-TCDD is released from some facilities (16).

High temperature is required to adequately destroy the dioxins and furans, and new incinerators are designed to achieve this. However, secondary formation can occur in the burner or stack as the gases cool, and chlorine has a chance to react with phenolics such as lignin.

Mercury: Combustion of municipal solid waste is the largest source of air emissions of mercury in urban areas, followed by burning of coal and oil for energy generation and by sludge incineration (26).

The main sources of mercury in the waste

stream are batteries (84%) and fluorescent lighting (6%) (26). These can be removed and the mercury reprocessed. If they are not, significant quantities of mercury may be released. In New York City, mercury produced the highest hazard index (5), and of the list of about 50 pollutants examined, only mercury contributed significantly to citywide environmental loading. Although airborne levels of mercury were not high enough to be directly toxic, they entered aquatic ecosystems and bioaccumulated in food chains such that a subgroup of people consuming seafood from these waters would have significant exposure (5). Some recreational and subsistence fishermen actually consume significant amounts of fish from the New York harbor areas (27, 28).

Cadmium: Cadmium is present in many metal-containing materials, particularly certain batteries, and incineration is a significant source of atmospheric cadmium, particularly in areas which are not also contaminated by smelters.

Chromium: Incineration is a significant source of chromium emissions. Various reports on emissions differ on whether the chromium is in the trivalent or hexavalent form. If the chromium is emitted in carcinogenic, hexavalent form, it becomes the main contributor to the risk assessment. However, even trivalent chromium is readily converted to hexavalent chromium in soil in the presence of manganese dioxide which is abundant (29).

Risks from Different Types of Incineration.

A variety of factors determine the amount of hazardous emissions from incinerators, including features of design, operations, and feed stock (2, 9, 30).

Mass-burn (waste-to-energy): medium to high contribution to air pollution risk. If operated according to specifications, the protection index for most metals exceeds 100, but for oxides of nitrogen the protection index was only 15. This in turn can be expected to contribute to increased ozone levels.

Refuse-derived fuel (waste-to-energy): medium to high contribution to risk. This form of incineration potentially contributes to significant air pollution, but there are few data to adequately characterize emissions from such facilities.

Sludge incinerator: medium to high contribution, depending on the source of the sludge. Again, too little data are available to predict its contribution, but the protection index for nickel was only 7, and for arsenic, only 10 (5).

Medical incinerators: These incinerators potentially contribute significantly to airborne lead and to odor. Calcium oxide and carbonate are

used for odor control. Large regional incinerators are being planned to reduce the number of point sources. The available data and resultant modeling produced protection indices of only 4 for hydrogen chloride, 7 for oxides of nitrogen, 9 for dioxin, and 13 for cadmium. Significant technological improvements are required for these facilities, which are necessary to replace obsolete or proscribed hospital incinerators. Protection indices should at least exceed $10\times$.

Regulations

Air pollution from incinerators is regulated in a variety of ways. Some air pollution standards governing emissions from industries and power plants are health based, but in fact many are based strictly on technological considerations, such as the best available control technology (BACT) and the lowest achievable emission rate (LAER). As technology changes, as source reduction and source separation of wastes improve, states will regulate more pollutants to achieve even lower levels than at present. This creates a moving target for facility designers.

Siting of Incinerators

Incinerators, whether for solid or hazardous waste, inevitably elicit the not-in-my-backyard (NIMBY) syndrome (12), and air pollution and health issues, particularly dioxin emission, form the basis for opposition. Builders of incinerators argue that having an incinerator as a neighbor is 10,000 times safer than driving a car and 100 times safer than riding a bicycle, but such risk comparisons neither impress an angered community nor assuage its anxieties. The incinerator is viewed as having no benefit to the neighbor, unlike the car or bicycle.

One way of preventing health risks and concerns regarding incineration is to situate noisy and smelly facilities at an adequate distance from residential areas, other workplaces, and recreational areas, and to assure that impact on transportation is minimized—extremely difficult goals in urbanized areas, particularly in the megalopolis.

One proposal to incorporate into siting negotiations is for incinerator builders to post a bond with the nearby community to provide for independent assessment of performance and emissions coupled with the ability to immediately shut down and upgrade a facility performing significantly below specifications.

Conclusions

This paper has emphasized public health concerns related to the potential toxic emissions to air or water from alternative waste management facilities. In addition, aesthetic, economic, traffic, and other considerations have a profound impact on the willingness of a community or governmental jurisdiction to accept any kind of waste management facility.

Public policy should provide for health as well as economic auditing, and there should be financial incentives and disincentives to encourage source reduction and to encourage waste producers, haulers, and managers, to choose socially and environmentally desirable approaches.

Developing and evaluating a comprehensive waste management system requires

- confidence that the existing health and environmental guidelines are adequately protective
- a procedure for assuring that all components are maintained and operated according to specifications
- enforcement if the system or any part of it should prove noncompliant

Such an analysis necessarily assumes that facilities will be designed, built, maintained, and operated according to adequately protective specifications in a fashion that will allow them to achieve or better the emission estimates. As in most situations, the potential for significant occupational exposure is higher than for community exposure, and clearly attention should be paid to assuring that workers are adequately protected, even when a particular scenario does not reveal much risk to the community at large.

Regardless of the choice of technology, siting of a facility should take into account:

- Site selections which minimize proximity to residential areas and to unrelated areas of employment, and which also minimize exposure to sensitive terrestrial and aquatic ecosystems.
- Adequate site size to minimize exposure to surrounding communities.
- Adequate distance from high-rise buildings to reduce the impact on elevated receptor populations.
- Adequate stack height (requires avoiding areas with Federal Aviation Administration regulations on stack heights).
- Involvement of the community in the earliest stages of planning, including a clear presentation of cost-benefit and risk-benefit considerations.

- Assurance of adequate maintenance and safe operation backed up by posting a bond with the community allowing it to monitor and even shut down a faulty facility.

The decision to build an incinerator must be made in the context of a long-term, comprehensive waste reduction program.

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Human Exposure to Toxic Materials

The New York–New Jersey Metropolitan Region

C. R. KRISHNA, PH.D., R. C. KLEIN, M.S., KEITH W. JONES, PH.D., N. L. CLESCERI, PH.D., AND E. A. STERN

PEOPLE living in the New York–New Jersey metropolitan region around New York City are exposed to toxic chemicals or elements that occur naturally or are produced as a result of human activity. Radon is an example of a naturally occurring toxic element produced by the radioactive decay of naturally occurring elements. Polychlorinated biphenyls (PCBs), polychlorinated dibenzodioxins (PCDDs), and polychlorinated dibenzofurans (PCDFs) are examples of toxic chemicals historically produced and used in industry. Air pollution by particulates, such as SO_x and NO_x and other petroleum combustion products, is produced by the operation of internal combustion engines, home heating furnaces, industrial and utility combustion systems, and many other devices.

Human exposure to these materials comes about through the air we breathe, the water we drink, and the food we eat. As an example, consider some of the routes for exposure to lead. Lead has been used in many industrial activities for years and is widely distributed in urban regions. Operation of facilities for manufacture of lead-acid batteries directly exposes workers to airborne particles and has often brought about substantial pollution of the surrounding land. Run-off carrying lead from the site then pollutes streams, rivers, and estuaries and enters the food chain through agricultural produce or fish and shellfish taken from affected waters. The general

population is at risk from inhalation of lead contained in particles of lead-containing paint. The urban water supply can be affected by lead contained in components of the water system and by different types of bacteria.

The consequences to human health from these exposures are substantial. Environmental exposures have been linked to cardiovascular, pulmonary, reproductive, and neural dysfunction, immune system disorders, cancer, and developmental problems. It is obviously important to emphasize improved medical treatment of conditions which may be wholly or partially the result of environmental exposures. It is equally important to work to reduce the levels of exposure of the population by improved environmental regulations, making changes in the materials and methods used in manufacturing, and the ways in which homes and offices are operated.

The actual implementation of change is difficult because of the complex nature of the urban system. Changes which reduce a contaminant can bring about deleterious effects elsewhere which negate the benefits gained from the original action. Environmental, health, and economic needs must be considered in an integrated way if overall progress is to be made. Creation of new organizational teams bringing together all the skills and interests that represent the various interests are needed. The participation of environmental and occupational physicians and epidemiologists as part of this grouping is important.

Problems related to contamination of sediments in the Port of New York–New Jersey are a current illustration of situations and conflicts that arise in attempts to ameliorate environmental degradation that ultimately relates to clinical practices in environmental and occupational medicine. An outline of the problem is given be-

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Address reprint requests to Keith W. Jones, Brookhaven Rensselaer Environmental Partnership, Brookhaven National Laboratory, Building 901, Upton, NY 11973-5000.

low. The intent is to show the complexity of the problem and to touch on potential health-related concerns.

Contaminants

Airborne. Airborne contaminants are a major pathway for human exposure in urban areas. The magnitude of the problem in the New York–New Jersey region is shown in the estimates of emissions from point and area sources (Table 1) (1). Airborne emissions are directly related to problems of contaminated sediments. First, pollutants can be transferred from air to water in the port region and thence to the sediments. Second, decontamination of dredged material (and sewage sludge) using several different methods can result in air emissions of contaminants that contribute to the overall air quality problem in the region. Problems that stem from use of incinerators have been considered in a joint study (2) of the United States Environmental Protection Agency (USEPA), the New Jersey Department of Environmental Protection and Energy (NJDEPE), and the New York State Department of Environmental Conservation (NYSDEC).

A recent study (3) from the Harvard School of Public Health highlights the health consequences of fine particulates (defined as particles with aerodynamic diameters less than 2.5 μm) that are present in metropolitan area atmospheres. The fine particles are derived chiefly from fossil fuel combustion sources and their size range contributes to their deep penetration into the lung. They can also act as carriers for potentially harmful chemicals.

In Soil. Soil contamination is highly variable and it is not possible to give an overall view of concentrations of particular chemicals or compounds that are representative of the region as a whole. Two examples can be cited. In the Jersey City region, the plating industry was a heavy user of chromium, which brought about contamination of soils and ground water (4). Chemical manufacturing in Newark on the Passaic River resulted in contamination of soils and sediments with high levels of dioxins. Surface runoff and contamination of ground water ultimately leads to transfer of the contaminants from soils to the harbor environment, including water and sediments.

In Sediment. Contaminants in the sediments are the result of contributions from many sources (5), including runoff from farms and lawns in rural, suburban, and urban areas. Discharges from factories to the atmosphere, water, or soils ulti-

TABLE 1
Summary of Atmospheric Emissions in New York and New Jersey (metric tons/year)

Substance	Point Sources		Area Sources	
	NY	NJ	NY	NJ
SO ₂	760,082	233,574	99,994	69,202
SO ₄	23,645	6,520	17,767	12,855
NO	279,527	127,777		
NO ₂	8,372	4,623		
NOX			407,276	258,647
Pb	16	0	1,140	640
CO	113,978	83,692	4,213,753	2,005,206
HCL	9,200	2,442	63	112
HF	1,875	302	5	24
NH ₃	3	12	12,663	62
TSP	245,892	98,206	505,141	275,792
Ca	1,367	37		
MG	1,144	24		
NA	548	11		
K	310	6		
VOC	90,149	104,827	971,333	536,991
THC	141,636	119,935	1,020,955	571,389

VOC, volatile organic compounds; TSP, total solid particulates; THC, total hydrocarbons.

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mately are contributors. Sewage processing facilities must deal with large volume discharges of both solids and liquids. Atmospheric contributions are responsible for a substantial part of the input to the harbor.

The types of contaminants found in sediments include the full spectrum of metals and chemical compounds used in the daily activities of an industrial society. Typical values (6) are available (Tables 2, 3) for sediments taken from four different sections of the Harbor: the Gowanus Canal and Newtown Creek in New York, the Arthur Kill lying between New York and New Jersey, and upper Newark Bay in New Jersey. An overall evaluation of existing data for the Harbor has been presented by Squibb et al. (7)

A specific evaluation of potential hazards from high levels of mercury (Hg) contamination in the region of Arthur Kill, Newark Bay, and the Passaic River has been carried out by Gillis et al. (8). They list a number of sources for the Hg contamination, including "metallurgy facilities, smelters, scrap metal yards, agricultural and urban storm water runoff, power plants, pulp and paper mills, textile manufacturers, petroleum refineries, municipal waste disposal facilities, combined sewer outfalls and stormwater bypasses." Results found for Hg concentrations in sediment samples taken in the area show a maximum 9.8 mg/kg (dry weight). They reported evidence for effects on health of fish, even though the concen-

TABLE 2

Metal Concentration in Sediments from the Gowanus Canal and Three Locations in the Port of New York–New Jersey: Upper Newark Bay, Arthur Kill, and Newtown Creek

Metal	Concentration (mg/kg dry weight)*			
	Newark Bay	Arthur Kill	Newtown Creek	Gowanus Canal
Antimony	NA	NA	NA	<21
Arsenic	9–17	17–25	5–33	10
Beryllium	NA	NA	NA	1
Cadmium	1–2	1.5–3	1–20	11
Chromium	175	161	305	151
Copper	105–131	178–304	61–770	630
Lead	109–136	111–261	68–554	1,343
Mercury	2–3	2–4	1–3	3
Total				
Nickel	33–40	20–60	12–140	88
Selenium	NA	NA	NA	2
Silver	2–4	2–5	2–3	21
Thallium	Na	NA	NA	<42
Zinc	188–244	230–403	104–1,260	1,130

NA, not available.

* The metal concentrations for Newark Bay, Arthur Kill, and Newtown Creek were obtained from the U.S. Environmental Protection Agency (private communication from Audrey Massa, 1994) and, for the Gowanus Canal, from Hazen and Sawyer, Inc. (private communication from Robert Smith).

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tration levels were below 1 ppm. They suggest that the mercury concentrations may be high enough to pose a threat to human health and that additional sampling and better understanding of the chemistry and transport of Hg are needed before final conclusions can be drawn.

Dredging

Economic Necessity in the Port of NY–NJ.

Dredging of the Port of New York–New Jersey is necessary to maintain adequate depths in shipping channels. The need is accentuated by the slow shift to use of vessels with increasing drafts, requiring deepening of the channels beyond their historic depths. At the same time, restrictions on ocean disposal of dredged materials have been increased by more stringent regulations based on bioaccumulation and biotoxicity tests.

The port is now in danger of becoming economically uncompetitive in comparison with other ports along the Atlantic coast. Reduction of commerce handled through the port will have a severe impact on the economy of the bistate region. There is a direct impact on revenues and jobs based directly in the port. It is estimated (9) that the total economic activity generated is \$20 billion per year and that this is responsible for more than 180,000 jobs.

Reduction of the port activity implies that other means will be needed to transport needed materials to the region. Offloading cargoes from larger to smaller ships, either at a port location or elsewhere, will raise shipping costs. If traffic is diverted to other locations and moved to New York–New Jersey by rail or truck, considering that the cargo of one ship is claimed (9) to represent the capacity of 1000 rail cars or 2000 trucks, it is plausible to believe that large strains would be placed on the regional infrastructure. There would clearly be both economic and environmental consequences that would have a strong impact on the region.

Management of Dredged Material. The traditional method for disposal of dredged materials has been ocean dumping, which has become increasingly restricted in use because of the difficulties in obtaining the necessary permits. An alternative method is urgently needed for disposal of that fraction of dredged materials not suitable for ocean dumping. Several possible methods have been mentioned (10). They include the use of "borrow pits," subaqueous pits filled with contaminated dredged material and capped with clean material to prevent the dispersal of the contaminants. A more sophisticated approach is to use containment islands which are designed with impermeable barriers to prevent fluid flow between the dredged materials and the surrounding waters. Finally, application of decontamination technologies that remove the contaminants from

TABLE 3

Concentrations of Volatiles, PCBs, and Other Properties of Sediments from the Gowanus Canal and Three Locations in the Port of New York–New Jersey: Upper Newark Bay, Arthur Kill, and Newtown Creek.

Contaminant	Concentration (mg/kg dry weight)*			
	Newark Bay	Arthur Kill	Newtown Creek	Gowanus Canal
Benzene	NA	NA	NA	8
Toluene	NA	NA	NA	20
Chlorobenzene	NA	NA	NA	9
Ethylbenzene	NA	NA	NA	79
Total xylene (o,m,p)	NA	NA	NA	54
Total PAHs	NA	NA	NA	24742
Corrosivity (ph)	7.06–7.61	7.08–7.47	7.38–7.76	9
Ignitability (C)	NA	NA	NA	>100
Total available cyanide	NA	NA	NA	<.3
Total available sulfide	683	1820	4850	475

NA, not available; PAHs, polynuclear aromatic hydrocarbons.

* Concentrations for Newark Bay, Arthur Kill, and Newtown Creek were obtained from the U.S. Environmental Protection Agency (Audrey Massa, private communication 1994) and, for the Gowanus Canal, from Hazen and Sawyer, Inc. (Robert Smith, private communication, 1994).

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the dredged materials may be able to clean those dredged materials so that they can be disposed of in the ocean, landfill, or through some beneficial reuse. The challenge, regardless of the approach chosen, is to find a method or methods that can be applied to solve the problem of disposal of dredged materials at an economically feasible cost.

No matter what method is chosen for disposal, efforts to reduce emissions and discharges which pollute waters, soils, and atmosphere with toxic materials are very important. In the long term, the quantity of contaminated sediments will decrease, and the problem of disposal will steadily decrease.

Methods for Decontamination. Methods for decontamination of dredged materials are varied. Each can be evaluated for effectiveness in contamination reduction. In addition, each represents a large-scale industrial process with its own inherent potential for emissions unsatisfactory from an environmental standpoint, and for other hazards important from an occupational safety standpoint.

A simple example would be the use of mechanical separation of large and small particle types. The rationale for this is the higher concentration of contaminants generally found in the fine particles (clays) than in larger ones (sands and gravels). From an environmental standpoint, there could be emissions of fine particles into the atmosphere and the need to control odors. Workers will be exposed, and proper industrial hygiene measures must be taken to protect them during the operation.

More complex treatment methods are also used. For example, the application of high temperatures to these materials can convert them into a glasslike matrix which can effectively bind toxic metals. At the same time, the temperatures are high enough to bring about the destruction of organic materials. Again, it is necessary to consider all discharges to the environment which could in the end be harmful and to take the necessary operational precautions. Other decontamination technologies include stabilization of the materials in a cementlike matrix, washing with chemicals to remove surface contaminants, use of bacteria to destroy organics or to concentrate metals.

It can be seen that none of these methods is a panacea. All are moderately large scale manufacturing processes that must be operated carefully so as not to damage the environment or to cause a hazard to human health, either in the

general population or in occupationally exposed workers.

Implications for Environmental and Occupational Health

Work on dredged materials is important since it affects the economic viability of the Port of NY-NJ and can have implications for the health of the environment and for the health of humans. The clinical physician should be aware of the complexity of the environmental problems posed by conditions in NY-NJ and how they relate to human health. Some of the general problems have been mentioned above. Physicians dealing with patients from a group which does subsistence fishing might consider the possibility of illness related to high levels of toxic chemicals or metals in the fish. In addition, if a new industry develops in handling and treatment of contaminated dredged materials (or soils), it would be good to be informed about the concentrations of contaminants and possible health problems relating to exposures.

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Alternative Sources of Risk Estimates for Cancer Effects of Radiation

ALICE STEWART, M.D.

GUARDIANS OF THE NUCLEAR INDUSTRY include an International Commission on Radiological Protection (ICRP), a United Nations Scientific Committee on Effects of Atomic Radiation (UNSCEAR), and a U.S. Committee on Biological Effects of Ionizing Radiation (BEIR). At this level there is general agreement that the best method of risk estimation for cancer effects of radiation is by linear extrapolation from high-dose effects, and that the best source for the effects of high, medium, and low doses is a life-span study (LSS) cohort of A-bomb survivors (1, 2). Therefore, although there are alternative sources of human data, as well as more direct estimates of low-dose risks, A-bomb data, as interpreted by the Radiation Effects Research Foundation (RERF), are still the mainstay of all radiation safety regulations.

Alternative sources of human data include the Ankylosing Spondylitis Survey, or ASS data (radiotherapy) (3, 4); a survey of nuclear workers at Hanford, or Hanford data (occupational exposures) (5–10); and the Oxford Survey of Childhood Cancers, or OSCC data (fetal irradiation) (11–13). From Hanford and OSCC have come risk estimates that are much higher than any RERF estimates (8, 9). But with much uncertainty about the correct interpretation of Hanford data (14) (and no discrepancy between the RERF and ASS estimates) it was possible for ICRP and other groups to continue ignoring the higher estimates. In medical circles, the RERF basis of radiation safety regulations is so taken for granted that even radiologists are unlikely to have heard of the Hanford controversy or to have been told that behind warnings about not x-raying pregnant women lie risk estimates based not on A-bomb data but on OSCC data.

From the Department of Public Health and Epidemiology, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK. Address reprint requests to the author at that address.

Human Surveys Important to Risk Estimates

Hanford data are no longer the only source of risk estimates for nuclear workers that differ significantly from RERF estimates, but other worker cohorts that now fall into this category (15, 16) are included among ones recently assembled by the International Agency for Research on Cancer (IARC) for the express purpose of testing the general validity of A-bomb data (17). Therefore, most of the reasons for and against continuing to use RERF risk estimates as the basis of radiation safety regulations can be found in the following sets of human data.

A-Bomb Data, or the Survey of Japanese A-Bomb Survivors. The first postwar census of Japan was held on October 1, 1950. This provided the Atomic Bomb Casualty Commission (ABCC) with an opportunity to identify two study populations of A-bomb survivors and launch the surveys that later became the responsibility of RERF (18–22). In addition to the LSS cohort, which eventually included 80,000 persons born before the two exposure dates in August 1945 who subsequently had two estimated doses (T65 and SD86) (18–20), there was a much smaller cohort consisting of exposed persons born in the next nine months (21, 22). From this in utero cohort has come evidence of teratogenic as well as carcinogenic effects of the A-bomb radiation. But, unlike the OSCC data for prenatal x-rays, it has produced no evidence of a juvenile cancer risk and, unlike the LSS cohort, it has produced no evidence of a special association between radiation and leukemia.

For the LSS cohort, principal findings were:

- a noncancer death rate that always remained close to expectations based on national statistics, and never showed any signs of a linear trend with dose
- a cancer risk that was greater for exposures

before 50 years of age than for exposures at older ages, and greater for myeloid leukemia than for other neoplasms

- much shorter intervals between exposure and death from leukemia than from other cancers
- extra deaths from aplastic anemia among the high-dose survivors

The last finding—which disobeys the rule of no dose-related effects in noncancer deaths—is replicated in ASS data but not in Hanford or OSCC data (see below). It is ignored by RERF, on the grounds of difficulty in distinguishing between leukemia and other intractable blood diseases (18, 19)—yet later deaths from aplastic anemia clearly form a continuum with early deaths from outright destruction of the reticuloendothelial system (RES) (23).

Hanford Data, or the Survey of Workers at the Hanford Nuclear Facility. The source of Hanford data is a study population consisting of 36,000 workers (mostly men) who, between 1944 and 1978, were employed for varying periods of time on tasks requiring the wearing of personal dosimeters. For these workers, the total cumulative dose was 831 Sv and, by 1987, there had been at least 1,732 cancer deaths. The first suggestion of a cancer risk came in 1977, when Mancuso, Stewart, and Kneale (MSK) compared the doses of 442 men who had died from cancer with the doses of 1,742 workers who died of other causes and found that the former had, on average, higher cumulative doses than the latter (8). Since this difference was statistically significant, and was the result of doses received more than ten years before death, it became the basis of a risk estimate much higher than any equivalent RERF estimate. The “rogue” estimate was ignored by ICRP and others for two reasons:

- there were no signs of the special leukemia effect clearly seen in A-bomb data
- there was a distinct impression of a smaller risk from exposures at ages under 50 years than from exposures at an older age—the opposite of what was found in A-bomb data

Since 1977 there have been confirmations as well as rebuttals of these MSK findings (14). And with Gilbert et al. constantly finding low rates of cancer mortality for Hanford workers, and failing to find any evidence of a dose-related cancer risk (5–7), it was possible for ICRP and others to maintain their policy of ignoring anything that differed significantly from RERF estimates.

List of Acronyms

ABCC	Atomic Bomb Casualty Commission
ASS	Ankylosing Spondylitis Survey
BEIR	U.S. Committee on Biological Effects of Ionizing Radiation
IARC	International Agency for Research on Cancer (World Health Organization)
ICRP	International Commission on Radiological Protection
LSS	Life Span Study Cohort of A-bomb survivors
MRC	Medical Research Council
MSK	Mancuso, Stewart, and Kneale
ORNL	Oak Ridge National Laboratory
OSCC	Oxford Survey of Childhood Cancers
RERF	Radiation Effects Research Foundation
RES	Reticuloendothelial system
UNSCEAR	United Nations Scientific Committee on Effects of Atomic Radiation
Sv	Sievert: a measure of radiation dose equal to 100 rem
T65	Original estimates of A-bomb doses (1965)
SD86	Revised estimates of A-bomb doses (1986)

OSCC Data, or the Oxford Survey of Childhood Cancers. The source of OSCC data is a nationwide survey of cancer deaths in children and juveniles which, over a period of nearly 30 years, continued to yield evidence of

- a cancer risk associated with radiography of the pregnant mother in spite of a steady decrease in the relatively small doses needed for these x-ray examinations

Other findings of this survey include

- evidence of a greater risk from exposures in the first trimester than from exposures in the third trimester
- the same risk for leukemia and other juvenile neoplasms
- mounting sensitivity to infections during the latent phase of leukemia (24)
- a naturally clustered distribution of childhood leukemias with lower death rates in large cities than in sparsely populated regions
- evidence that in utero exposure to background radiation is a numerically important cause of childhood cancers (13)

IARC Data, or an Analysis of Pooled Data from Several Nuclear Facilities. The unusually large set of occupational IARC data is the result of IARC combining seven cohorts of nuclear workers from three countries: the United States, Canada, and Britain (17). In the pooled data are three study cohorts which, as separate entities, had already produced evidence of a dose-related cancer risk greater than any RERF equivalent—the cohorts of Hanford (10), of the Oak Ridge National Laboratory (ORNL) (15), and of Sellafield (16). From the single large cohort has come evidence of a few extra leukemia deaths, but there were no signs of any general cancer risk, and even for leukemia, the estimated excess relative risk was no higher than the RERF estimate. The final conclusion of IARC—that RERF estimates for A-bomb survivors are directly applicable to nuclear workers—is based on an untested assumption of comparable standards of dose estimation in each facility (17).

Ankylosing Spondylitis Survey (ASS Data). In 1950 a roundup of all patients treated in one radiotherapy clinic in Holland revealed five cases of leukemia among men with ankylosing spondylitis. There followed a systematic follow-up of all such treatments in Britain by the Medical Research Council. This MRC survey revealed an excess of deaths from three causes (3):

- leukemia
- aplastic anemia
- ulcerative colitis

There were later attempts to whittle down the number of deaths from aplastic anemia (by claiming misdiagnoses), and the extra deaths from ulcerative colitis have never been ascribed to the radiation exposures. However, with exceptionally high doses to the colon as well as the spine (and thousands of A-bomb deaths from fulminating infections of the bowel) (23), there remains a distinct possibility of two late effects of radiation other than cancer.

Three Hypothetic Suspicions and Reasons for Them

What follows are some of the reasons for the following suspicions:

- at high dose levels, cancer was not the only late effect of the A-bomb radiation
- the normal noncancer death rate of the LSS cohort was an artefact caused by a masking of

chronic effects of marrow aplasia by late effects of survival of the fittest

- deaths during the latent phase of slow-growing cancers (“competing causes of death”) are the reason why relations between age at exposure and subsequent cancer risk were so different for A-bomb survivors and nuclear workers, as well as the reason why late effects of in utero exposure to A-bomb radiation and diagnostic x-rays were so different

Comparisons between OSCC data and A-Bomb Data. As early as 1958, OSCC data were showing that children who had recently died from malignant neoplasms had been x-rayed before birth more often than had live controls, and that the extra x-rays were evenly distributed between leukemias and solid tumors (11). This nationwide survey eventually included all cancer deaths in persons younger than 16 years of age in the period 1953 to 1979 and the same number of live controls taken from regional registers of live births. In 1984, there were added to these 22,351 case-control pairs; regional statistics for births, deaths, and population density; and background radiation doses for each 10-km square of the national grid (12, 13).

From comparisons between OSCC data and A-bomb data has come evidence that late effects of fetal irradiation were very different in the two situations (25). Thus, in the British survey there was evidence of a cancer risk from background radiation as well as prenatal x-rays; also evidence that males and females were equally involved in a risk which was roughly the same for all types of juvenile neoplasms, and evidence that the peak incidence of the radiogenic cancer deaths was in children between 4 and 7 years of age. In the in utero cohort of A-bomb survivors there were no childhood leukemias, and only cohort members who reached 20–40 years of age had a significant excess of cancers. Furthermore, males were less affected (4 cases) than females (14 cases), and the extra cancers were unlike any seen in OSCC data.

According to Stewart and Kneale, possible reasons for the lesser involvement of males than of females in the cancer risk following in utero exposure to A-bomb radiation include an unusual number of male zygote deaths (direct radiation effect), and possible reasons for the absence of radiogenic leukemias include a high risk of fatal infections for several months after the bombing (indirect effect of the radiation via environmental damage) (25). In other words, the RERF assumption of no age-related effects of in utero exposures to A-bomb radiation could be a mistake—and a

false reason for concluding that the brain damage effects of radiation are not felt before 8 weeks of fetal age (23); and the general devastation could be the main reason why, following the in utero exposures to A-bomb radiation, there was no evidence of any special leukemia effects.

Comparisons between Different Interpretations of A-Bomb Data. The RERF assumption of equal involvement of all LSS age groups in late effects of the A-bomb radiation (20) could also be wrong, since an independent analysis of LSS data has revealed a strong concentration of survivors of high doses among the persons who were over 10 and under 50 years of age in 1945 (25). This finding makes it reasonable to assume age-related as well as dose-related effects; on this assumption, early deaths of A-bomb victims both reduced the slope of the dose-response curve for later deaths of survivors and disturbed the usual relationship between age and cancer risk. A recent test of this hypothesis showed that, when plotted against the radiation dose, LSS deaths from all causes except cardiovascular diseases and cancers produced a U-shaped curve with its lowest point close to the threshold dose for marrow aplasia (26). Stewart and Kneale also found several reasons why this biphasic curve was probably the result of selection effects of the early deaths being felt at dose levels that were too low to be much affected by the cell-killing effects of the radiation—though, at high dose levels, late effects of the cell killing were more than counterbalancing the beneficial effects of selection.

Though there have been many analyses of LSS data by RERF, none have shown the effects of separating deaths common only after this cohort had been in existence for ten years (deaths from cardiovascular diseases and cancer) from deaths exceptionally common before 1950 (deaths from all the remaining causes). By drawing this distinction, the independent analysis of LSS data discovered that what probably prevented exceptionally low rates of mortality (in spite of the strong selection in favor of exceptionally fit persons) was residual effects of reticuloendothelial system damage. Meanwhile, many RERF analyses have shown that one effect of this damage, extra deaths from aplastic anemia, continued long after 1950.

Comparisons between Different Interpretations of Hanford Data. By the time the above findings for A-bomb survivors were in print, Kneale and Stewart, who had been cut off from Hanford data after the MSK analysis of 1977 (8), were once again in a position to revive the Hanford controversy. There were now nearly four

times as many cancer cases as in the earlier analysis, and with these it was possible to produce evidence of a general cancer risk, and to show that

- exposures of people older than 50 years of age were especially dangerous
- intervals between cancer induction and death usually exceeded 14 years
- as a result of this delay, most of the extra radiogenic cancers occurred in persons older than 70 years of age
- the excess relative risk was no greater for leukemia than for other cancers

Gilbert et al. have continued to refute these findings. However, all epidemiologists who, in relation to occupational data, have both ignored “cancer modulating effects” of age at exposure and assumed uniform standards of dose estimation in all nuclear facilities (or “safe” pooling data from several sources) could be making a great mistake.

This forecast is the result of a recent analysis of data from five nuclear facilities in which the effects having one, two, or three distinct cohorts were compared. Both in three separate cohorts (Hanford, ORNL, and three smaller DOE facilities) and in a single cohort of “pooled data” there was evidence of a dose-related cancer risk much greater than equivalent RERF estimates. But, in addition, there were significant differences between the pooled and unpooled data that were clearly the result of different standards of dose estimation in each facility. This analysis has now been published (26A). It includes several findings that support a previous impression of much better recording of Hanford doses after than before 1960 (27), and thus provides a further reason for doubting whether the IARC analysis of pooled data was of any use in settling the controversy about whether RERF estimates are or are not directly applicable to low-dose exposures.

Special Effects of High-Level Radiation (Stewart Hypothesis). In the two surveys mainly or exclusively concerned with high-dose effects (A-bomb data and ASS data), there was evidence of an exceptionally strong association between myeloid leukemia and radiation, as well as extra deaths from the only distinctive effect of chronic marrow aplasia (aplastic anemia). Failure to find any evidence of these effects in Hanford or OSCC data is often seen by radiobiologists as a possible flaw in these data. But we all have also been asked (by an erstwhile physician) to consider the following high-dose scenario (28–30).

Following whole-body exposures to high

doses of A-bomb radiation, there must have been extensive damage to all soft tissues, especially the RES. This widespread damage would create a demand for all types of blood corpuscles (especially erythrocytes and myelocytes) which was difficult or impossible to meet. Any response from a greatly weakened RES would naturally reduce the risk of immediate death. But since this would involve intensive production of phagocytes, it would put myeloid components of red marrow at an exceptionally high risk of later, carcinogenic changes. Furthermore, by causing loss of immunologic competence, the RES damage would both aid and abet any cancer process (thus allowing extra deaths from myeloid leukemia to be the first sign of a general cancer hazard) and cause heightened sensitivity to infections (thus allowing the high-dose groups to be especially short of children and old persons). Finally, by causing difficulty in red-cell production, the same damage might cause extra deaths from aplastic anemia after as well as before 1950.

By allowing the normal noncancer death rate of the LSS cohort to be an artefact (caused by the opposite effects of selection and RES damage), the Stewart hypothesis would account for the U-shaped dose-response curve for all causes of death except cancer and cardiovascular diseases. It would also allow infection deaths to reduce the slope of the dose-response curve for cancer deaths, and thus allow the RERF method of risk estimation (by linear extrapolation of high-dose effects) to underestimate the cancer risk of low-dose levels. Finally, by allowing selection to have age-related as well as dose-related effects, the Stewart hypothesis would account for relations between age when exposed and subsequent cancer risk being totally different for nuclear workers and A-bomb survivors (31).

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Shaping Environmental Research:

The Lead Industries Association 1928–1946

RICHARD P. WEDEEN, M.D.

LEAD POISONING has been recognized for two thousand years, yet the metal remains a serious environmental hazard. The persistence of this preventable threat to public health stems from interactions between science, industry, and government. The subtlety of these interrelationships can be discerned from the minutes of the Lead Industries Association (LIA) annual meetings, quoted extensively below. The LIA was created in 1928 as a trade association to promote the use of and, in the era before the NIH, to support research on the health effects of lead. The association's actions in the second quarter of the twentieth century illustrate the pervasive influence of economic interests on academic priorities.

Industry and Science: Common Interests and and Cross-Purposes

The discourse between the LIA and the medical scientists who accepted industry sponsorship of their research reveals both common interests and cross-purposes. A symbiotic relationship between the LIA and academia developed that led to the expansion of knowledge but, at the same time, constrained application of that knowledge in the interest of public health. The purpose of the industry's support of research is stated explicitly in the minutes of the LIA, prepared by Felix E. Wormser, secretary/treasurer of the Board of Directors. Wormser was a mining engineer and former executive of the St. Joseph Lead Company in St. Louis (1). His efforts on behalf of the lead industry were rewarded by President Eisen-

hower, who appointed him Assistant Secretary of the Interior for Mineral Resources. Through the LIA, Wormser endeavored to mold public opinion by shaping the direction of research. Consciously or not, distinguished scientists legitimized the LIA public relations effort. The minutes of the LIA provide candid insight into corporate goals in supporting medical research.

Modern Knowledge of Dangers of Lead. Wormser was not ignorant of the hazards of lead poisoning, which had been the subject of medical commentary for two thousand years. The debate had been presented in modern terms in the eighteenth century. The danger of the ingestion of lead paint by children was described in 1776 by Dr. John Fothergill, an eminent London physician and benefactor of America's first medical school, in Philadelphia (2). Noting several unusual sources of lead poisoning just nine years after Sir George Baker's seminal description of the causal role of lead-contaminated apple cider in Devonshire colic, Fothergill described an eight-year-old boy "complaining of pains in his belly and stomach. . . . On examining further," he reported, "I found, also that he had got a trick of being almost continuously wetting his pencils in his mouth, while there was paint on them" (3). This may be the first reported case of lead poisoning from childhood pica.

The widely read English translation of Tanquerel des Planches' monograph "Lead Diseases" in 1850 reacquainted members of the American medical community with the dangers of lead poisoning (4). In 1852, a Committee on Zinc Paint established by the Board of Assistant Aldermen of New York City passed a resolution urging the use of zinc instead of lead-based paints for "roofs, iron works and places exposed to impure air" (5). The committee's efforts had been initiated by the New Jersey Zinc Company, which urged that

From the Veterans Affairs Medical Center, East Orange, NJ, and the Depts. of Medicine and of Preventive Medicine and Community Health, University of Medicine and Dentistry of New Jersey—New Jersey Medical School.

Address reprint requests to the author, Associate Chief of Staff, Veterans Affairs Medical Center, 385 Tremont Avenue, East Orange, NJ 07018-1095.

zinc-based paint replace lead-based paint in order to prevent lead poisoning.

The danger of lead paint to children was further brought to medical attention by an epidemic of lead-poisoning in Queensland, Australia, at the turn of the nineteenth century (2). Seventy-five years of study of these children established hypertension and kidney disease in young adults ("Queensland nephritis") as a consequence of the ingestion of lead paint in childhood. Between 1922 and 1931, nine countries banned interior lead paint in housing to protect children, but the United States did not follow their example until 1970.

For most of the present century, medical science accommodated lead industry interests. Financial support for research was funneled through industry-controlled associations. There was no public outcry against environmental lead.

Industry Shaping of the Research Agenda. Central to the LIA public relations effort was Robert A. Kehoe, M.D., who—through his simultaneous positions as director of the Kettering Laboratories of Applied Physiology at the University of Cincinnati and medical director of the Ethyl Corporation—exerted considerable influence on the direction of lead research for six decades. Although some of the industry-controlled organizations adopted official-sounding names—"Industrial Hygiene Association," "American Conference of Governmental Industrial Hygienists"—the LIA was an acknowledged trade association. It shaped the research agenda by funding scientists who assuaged public fear of lead poisoning. The success of the effort to guide the development of new knowledge is documented in William Graebner's essay "Private Power, Private Knowledge, and Public Health: Science, Engineering and Lead Poisoning, 1900–1970" (1).

Common Interest: Further Research. Regardless of the conclusions drawn from any specific research on lead, both industry and academia could agree that more research was needed. In rejecting the causal relationship between lead poisoning and kidney disease developed in Australia, Wormser at the annual meeting of the LIA on November 27, 1945, could quote with satisfaction a statement by the Committee on Lead Poisoning of the American Public Health Association:

even in the case of children the production of chronic nephritis, perhaps better described as diffusely scarred kidneys, cannot be certainly attributed to the effects of an episode or multiple episodes of lead poisoning. The facts in these matters must await further careful clinical investigation.

It served industry's purpose to defer mandates for preventive action. It served the scientists' purpose to increase research funding. The privilege of discovering truth is reserved for those who first of all support themselves and their research enterprise.

Research as Public Relations. At the annual meeting of the LIA Board of June 16, 1933, Wormser summarized the industry's interest in scientific research. From its inception in 1928, the LIA supported research at Harvard under the direction of Joseph Aub because

Only with accurate knowledge of lead are we able to combat many of the unwarranted attacks on lead and I hope the Board will see the wisdom of continuing and even increasing our medical research. In this connection I would like to point out that Dr. Aub's fund expires on July 1st.

Wormser discussed the value of research in stopping public assaults on lead-based pesticides at the annual meeting of the LIA Board of Directors on June 5, 1935. "It is quite possible," the Board's secretary/treasurer noted, "that some jointly supported medical research will be undertaken that will not only help in the spray residue problem but will also help to answer some other attacks on lead."

At the annual meeting on June 13, 1935 held at the Waldorf-Astoria in New York City, Wormser reported:

We are constantly investigating alleged cases of lead poisoning and endeavoring to correct misstatements about lead poisoning, to calm misapprehension about the toxic properties of the metal and to accumulate all possible material of scientific value to help us in our efforts.

At the request of Dr. Aub of the Harvard Medical School and his associate Dr. Fairhall, we are contributing \$10,000 to Harvard College.

At the annual Board meeting of March 16, 1937, Wormser noted Dr. Fairhall's professional advancement with obvious satisfaction:

Dr. Fairhall, formerly of Harvard Medical School, who has long been associated with some of the lead work we have supported at Harvard, is now Principal Industrial Toxicologist for the U.S. Public Health Service. It seems to me that the more basic work is done in lead, the greater the evidence unearthed that lead is not the dangerously poisonous material so many incompetent critics claim it to be.

Fairhall's work for the LIA did not hinder his professional advancement. As chairman of the American Conference of Governmental Industrial Hygienists, he effectively used his influence to support manufacturers' goals. For example, he defended the threshold limit value for silica dust exposure, which was more effective in preventing economic burdens on industry than in preventing silicosis in the workplace (6).

At the annual meeting of May 3, 1938, Wormser complimented the Board on its success under his leadership:

An investigation of the lead content of evaporated milk, sponsored jointly by the Evaporated Milk Association, the International Tin Research and Development Council, and the Lead Industries Association, was concluded in 1937 by Dr. Fairhall and his findings published in November, 1937 issue of the *Journal of Industrial Hygiene and Toxicology*. The investigation gave solder, as used in sealing evaporated milk cans, a clean bill of health, greatly relieving the anxiety of the evaporated milk producers and helping to dispel for all time the efforts which are made periodically to discredit the use of one drop of solder for the purpose.

It was not until the 1980s that lead solder began to be voluntarily eliminated from evaporated milk cans, an effort that was completed in 1991.

At the December 21, 1937 meeting of the Board of Directors, Wormser had acknowledged his accomplishments:

Lead was given a clean bill of health. This is another illustration of the most effective way of dispelling some of the common misconceptions and attacks on lead.

He then expanded on the LIA's impact on the development of scientific knowledge:

It has been a routine occurrence to act for our industry in lead poisoning matters. I think that the situation, on the whole, is growing better as appreciation of Dr. Aub's and Dr. Kehoe's work on lead permeates the medical fraternity.

Just recently we had an opportunity to clear up a lead question with reference to the use of lead in drinking water. A professor in a southern university was prepared to write an article, for circulation among water works engineers, which would have been unfortunate for our industry and quite misleading from a scientific point of view. Through our efforts, this proposed publication has been substantially modified so that instead of injuring our industry it will present some reassuring facts.

I am glad to report that our relations with those agencies having to do with the public regulation of health matters, are extremely cordial and that a mutual confidence has been cultivated which speaks well for the solution of our future public health problems.

Wormser praised almost two decades of accomplishments by the Lead Industries Association at a conference on lead poisoning sponsored by the LIA in 1946 (7):

The observations and experiences of the industry indicate that various lead-consuming industries have been criticized for injuring public health only to have subsequent careful scientific investigation show the criticism to be undeserved. Incidentally, whenever criticisms are brought to the attention of the Lead Industries Association, its policy has been to recommend an impartial scientific investigation with full publicity to the conclusions no matter what the outcome. I cite briefly a few examples:

Solder in Milk Cans—One small drop of solder is generally used to close cans of evaporated milk. This use of lead

was attacked as being possibly a dangerous contaminant of the milk. Careful investigation at the Harvard School of Public Health was made, and the results gave lead a completely clean bill of health. Since the appearance of this study, the subject is apparently a closed one.

Spray Residues—... the apple industry succeeded in procuring a Congressional appropriation which was given to the United States Public Health Service to make a painstaking survey. The results are probably well known to my audience and are to be found in a Public Health Bulletin of the United States Public Health Service. It indicated, to say the least, that the fear expressed about spray residues was exaggerated. The report did not find a single case of lead poisoning among the 1231 persons examined, some subjected to high exposures of the spray.

Paint on Cribs and Toys—It is commonly believed that the eating of paint on cribs and toys has been a source of lead poisoning among children. Investigations of the Lead Industries Association cast grave doubts on most cases coming to its attention.

At the same conference, Robert Kehoe reinforced the view that blood lead levels over 50 $\mu\text{g}/\text{dL}$ were acceptable in industry by asserting that "the concentration of lead in the blood of the present day normal person varies between the limits of 0.01 or slightly less and 0.055 mg per hundred grams of whole blood" (8). Currently, the upper limit of normal for levels of lead in blood in children is 0.010 mg/dL.

Yet at times Kehoe balked at the heavy-handed approach Wormser took in attempting to discredit research that reported on the dangers of lead. In a January 29, 1945 letter to J. H. Shaefer, vice president of the Ethyl Corporation and a member of the LIA Board of Directors, Kehoe criticized the president of the LIA:

It is possible to pick numerous flaws in both his facts and in his reasoning. He is not aware of it, but he does not know enough about the basic information on this subject to discuss it critically and adequately.

The Scientists' View: Industry Serves Science. Where industry saw science as a useful public relations tool, the scientists saw industry as serving science. Industry funding of research was welcome. Key players in LIA strategy were Joseph C. Aub and Lawrence T. Fairhall, working in the laboratory of C. K. Drinker at the Harvard School of Public Health in the 1920s and '30s. By 1926, Aub was well aware that lead was stored in bone. In the definitive monograph of the period on lead poisoning, Aub interpreted bone storage of lead as a protective mechanism, a concept that the lead industry found to its liking (9, p. 76):

While stored in such a deposit the lead is apparently harmless, since the symptoms of plumbism are noted only when lead is generally distributed throughout the organism, as a result either of recent absorption from an external source, or of mobilization of a skeletal store.

Aub took a conservative view of the diagnosis of lead poisoning. He sought to explain disease in lead workers by factors other than exposure to lead:

appendicitis as well as colic can attack a lead worker and . . . those who have absorbed lead are not immune to cerebro-spinal syphilis [9, p. 117].

Certain races seem predisposed to lead poisoning. That Negroes are particularly susceptible has been stated by Edsall [David Edsall was dean of the Harvard School of Public Health]. . . . Children are said to be more easily poisoned than adults; and the presence of sterility and the frequent occurrence of abortion among women exposed to lead is evidence of their greater susceptibility [9, p. 195].

The concept of "greater susceptibility" of women was later used to rationalize "fetal protection" programs at Johnson Controls, Inc. that successfully excluded women from working in the lead industry until the practice was rejected by the U.S. Supreme Court in 1991.

Aub did not address the working conditions of employees. But in an appendix to the monograph (9), Alice Hamilton noted that acute lead poisoning had been reported in the United States in

at least 1770 cases in 19 plants employing some 7500 men and among these were 41 encephalopathies, 35 cases of paralysis and 16 deaths. The British rate for 1912 was only 1.8 per 100. Interviews with 167 smelter men, suffering from plumbism, showed that the majority . . . become intoxicated after only a short exposure.

Alice Hamilton was the first great American crusader for protection of workers. She was appointed the first woman on the Harvard Medical School faculty by Joseph Aub. Clearly Aub's tactful relationship with the LIA enabled him to support the efforts of Hamilton in reducing lead poisoning in the workplace, despite the unbending resistance of the LIA.

Although the LIA could not fully coopt the Harvard professors, the trade association did shape their research effort. With Joseph Aub and Lawrence Fairhall on the LIA research payroll, the camels were inside the tent. Potential debunkers were part of the industrial public relations team.

The Tone of the Discourse

After 1946 the discreet control of scientific research by the lead companies that had prevailed from the late 1920s was abandoned in favor of more strident efforts with the advent of government-supported research through the Na-

tional Institutes of Health. Scientists no longer dependent on corporate largess sometimes took less sympathetic views of the role of lead in society.

Herbert Needleman, M.D., a pediatric psychiatrist first at Harvard and later at the University of Pittsburgh, spearheaded an effort that provided a scientific basis for the removal of lead from gasoline. Needleman's work demonstrated that even low-level lead absorption (levels in blood less than 25 $\mu\text{g/dL}$) resulted in impaired neurobehavioral development in children (10). His conclusions have been widely reproduced and confirmed throughout the world. A decade of concerted effort by the LIA and other industry-supported associations failed to prove scientific misconduct by Needleman. A countersuit of his accusers by Needleman remains to be resolved.

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Occupation and Environment in Internal Medicine:

Sentinel Events and Trigger Questions

ELIHU D. RICHTER, M.D., M.P.M., AND PAUL BARACH, M.D.

Abstract

Patients who undergo sentinel events indicate a breakdown in the chain of prevention and protection. Because most work- or environmentally induced illnesses and disabilities produce nonspecific or late symptoms and signs, the search for exposures to physical, toxic, ergonomic, or sociopsychological events that induce these sentinel events has to be based on systematic investigative routine, and not on the physician's mere awareness. Routine use of five "trigger" questions to identify jobs, tasks, exposures, symptoms, and other persons at risk can be effective, quick, and inexpensive in the search for preventable illness related to work or environment in the sentinel patient, especially when illness persists, recurs, or progresses or occurs in others.

Sometimes, others can be helped when it is too late to do anything for the sentinel individual. This holds true for the relatively simple situations of one exposure and one outcome and for settings in which there are many exposures or many diseases in one or many patients.

The newer set of "clean" environments that include ergonomic and sociopsychological hazards and stress at the work-station have produced new sentinel events. Knowledge of the impact of macro-environmental hazards presupposes familiarity with their impact on individual risks. Using the sentinel event to promote prevention of hazardous exposures means opportunities for reducing unnecessary risk in individuals and small groups.

Opportunities for prevention arise when sentinel events occur at the time of exposure. Where there is latency between exposure and outcome, an anticipatory approach based on awareness of future risks from preventable current exposures is needed. The search for external exposures that have already occurred and for those that are preventable should be a routine part of internal medicine.

HOW MANY PHYSICIANS routinely ask patients about their exposures—current and past—at work, in the home, or in the community to physical, toxic, or ergonomic hazards? Some 300 years ago, Bernardo Ramazzini, the father of occupational medicine, recognized that his patients' ailments

derived not only from an imbalance of their internal "humors" (forerunners of the notion of constancy of the internal environment and of endocrinology) but their exposures to dusts, gasses, fumes, vapors, hot, cold, dampness, darkness, filth, repetitive motion, postural and lifting problems. As a routine, he asked his patients, What is your job? He also went out to see for himself what the exposures were. In doing both, he questioned the adequacy of the conventional medical paradigm ("balance of humors") for diagnosing and treating—but not preventing or ameliorating—the aches and pains, catarrhs, coughs, phlegms, colics, deformities, shrivelings, miseries, and sufferings of his patients.

From the Unit of Occupational and Environmental Medicine, Hebrew University–Hadassah School of Public Health and Community Medicine, Jerusalem, Israel. Address reprint requests to the author at PO Box 1172, Unit of Occupational and Environmental Medicine, Hadassah School of Public Health and Community Medicine, Hebrew University, Jerusalem, Israel.

Ramazzini's routine question, followed by what we would today call the walk-through survey or worksite visit, led him to recognize relationships between job, exposure, and disease that were better understood centuries later. Silicosis and mercury poisoning in miners, lead poisoning in potters, metal fume fever and "asthma" in tin-smiths, and vision problems in scholars are just some of the exposure-illness associations he recognized (1, 2).

Today, the term "internal medicine"—what is inside—no longer telegraphs the nonsequitur that equates locus of disease with source. This nonsequitur results from what Irving Selikoff, the mentor of many of us contributing to this issue, called the double-negative fallacy—exposure sources were not found because they were not asked for or searched for. The result: external causes—physical, toxic, or ergonomic—of illnesses seen in internal medicine and other clinical settings can be missed; exposures persist and the patients and their associates may continue at unnecessary risk, deteriorate and die, or carry on with preventable disabilities. Gennart et al. found that in an internal medicine ward of 200 patients, 21 (10.5%) were considered to have a primary illness probably or possibly related to their prior occupation, and 70 (8.9%) of 786 primary and secondary illnesses in 55 patients were similarly related to prior physical, chemical, or ergonomic hazards missed in routine diagnostic studies (3). Probes into tissues, cavities, recesses, cells, nuclei, genes, molecules, and atoms at best augment, but do not substitute for, systematic routine use of Ramazzini's two low-technology tools: the occupational history and the site walk-through. The search for past or current exposures becomes mandatory when patients' illnesses recur or disease progresses, or cancer appears.

Sentinel Events and Prevention

A sentinel event is a sign of breakdown in the chain of prevention and protection. Complaints, diseases, signs, disabilities, or deaths of patients that are plausibly related to exposures in their work, home, or community environment are occupational or environmental sentinel events (4, 5). Sentinel events, if shown to be related to an exposure, should trigger action by the physician not only to remove the individual from exposure, but to remove the exposure for this individual and for others as well. Those others may be colleagues at the same work site, those engaged in other, similar work processes; workers in an entire industry or families and entire communities of

those currently or ever exposed. Those exposed may be dispersed worldwide, as was discovered with the first reports of patients with angiocarcinoma who had been exposed to vinyl chloride in the fabrication process. Montague-Murray's autopsy report of pulmonary fibrosis in an asbestos worker in 1902 was an example of a sentinel event as was Lynch and Smith's 1935 report of carcinoma of the lung in "asbesto-silicocosis" (6). Both reports foreshadowed a century of too little and too late for hundreds of thousands of individuals—makers and users of asbestos at work, and those end users exposed to asbestos in place.

Nonspecific and Late Symptoms—The Rule and Its Exceptions. Nearly all toxic exposures produce symptoms and signs or diseases that are either nonspecific or appear years after the onset of exposure. However, certain "signal" cancers are exceptions to this statement; mesothelioma in persons with past exposure to asbestos, nasopharyngeal carcinoma in wood workers, and angiosarcoma from vinyl chloride exposure are sentinel cancers associated with exposure almost 100% of the time. Similarly, "signal" events of high specificity that may serve as early signs of exposure or disease are pleural thickening, calcification and plaques in chest x-rays of persons with asbestos exposure; highly elevated levels of zinc protoporphyrin in persons exposed to lead; Raynaud's disease in persons with vinyl chloride exposure or who use vibrating tools such as jackhammers; chloracne in workers and home end users exposed to TCDD (tetrachloro-dibenzo-p-dioxin), polychlorinated biphenyls (PCBs), or polychlorinated benzofurans (PCDFs) (7).

But the foregoing exceptions should not divert attention from the rule of nonspecificity. Added risk for lung cancer from exposures to vinyl chloride (4) was missed because lung cancer was more common and had a higher background risk than angiosarcoma, the signal tumor for vinyl chloride exposure.

Furthermore, tissue insults from repeated or prolonged toxic exposures leave residual functional, anatomic, metabolic, or genotoxic scars or impairments, which new research in biomarkers continues to discover. Therefore, even if variations in host susceptibility exist, the essential measures remain preventive: removal from exposure for the individual, and efforts to prevent or remove the exposure for others. Antidotes—methylene blue for methemoglobinemia, atropine and oximes for organophosphates, chelators for acute lead poisoning—may be life-saving in acute situations. But unless the person has been removed from exposure, analgesics for patients with head-

aches and fatigue associated with solvent exposures, steroid ointments for skin rash from nickel exposures, or bronchodilators for asthma in individuals exposed to toluene di-isocyanate are examples of medical mismanagement.

Trigger Questions To Detect Sentinel Events

Five simple "trigger" questions should, with some variation, be part of all routine history-taking:

1. What is your job/hobby and where do you work/live?
2. What do you do in your job? home?
3. What are you exposed to in your work? home? community?
4. When or where do your problems become worse/better?
5. Are there others at work/home/community with similar (or other) problems?

The first three questions search for exposures, the fourth explores the exposure-effect association, and the fifth searches for the possible epidemic for which the patient's complaint is the sentinel event. The last question opens the possibility to what we call quaternary prevention: preventing disease in others even if it is too late to help the sentinel patient.

The questions minimize the risk that the physician will miss clues to occupational or environmental causes of diseases, especially when the patient does not get better and illness recurs or progresses. The use of the sentinel event is essential to surmounting the two barriers to detecting the work- or environment-relatedness of disease: nonspecificity and latency of symptoms.

This paper shows how the use of these questions in sentinel patients led to the detection of previously missed occupational and environmental exposures, not only in the patients themselves, but in others in their work or community environment. Expanded checklists and questionnaires can be used to augment the questions if clues are suggested from the answers. These include checklists for sentinel events in relation to suspect exposures; job-exposure matrices, in which exposures are related to information on job description and job task; and material data safety sheets (8-13). The full spectrum of work-related disease has been reviewed elsewhere (14).

First encounters between patients and doctors in primary care or referral or hospital settings are frequently hurried or compressed, especially in public care facilities. Can the search for

exposures be "squeezed in" as part of the routine study, add to its sensitivity and specificity, and save unnecessary and expensive procedures—especially for the patient with a recurrent problem or the patient who does not recover? The Unit of Occupational and Environmental Medicine has been drilling medical students in the framework of their introduction to internal medicine—not in a separate course—in the routine use of the five trigger questions, with the aim of detecting sentinel events (occupational and environmental) within 45-60 seconds during the medical history.

Barriers to Detection. Our premise is that the entire medical network can be programmed to use these questions to find, evaluate, and help patients who have undergone these sentinel events. Even so, the thoughtful physician or health care worker will need to recognize that fear of job loss, false pride, distrust, or self-blame may serve as emotional or psychological barriers to full answers:

- **Objective barriers**
 - Nonspecific symptoms
 - Latent disease
- **Sociopsychologic barriers**
 - denial and false pride
 - fear: removal from job, job removal
 - guilt
 - distrust of physician

Malingering or fabricating are the exception, not the rule, because of the immediately devastating financial and emotional costs of unemployment, even for workers with dangerous jobs. This is only one of the reasons why work-related injury and disease are systematically underreported by surveillance and compensation systems (15).

In the six case reports below, the first three give examples of one-agent, one-place exposures. The last three present multiple-exposure, multiple-outcome situations. Each highlights the importance of each of the five trigger questions.

Case 1. What Is Your Job? Abdominal Cramps and Neurologic Complaints in a Firearms Tester. A 54-year-old man with a history of progressive abdominal cramps, alternating diarrhea and constipation, mood changes, irrationality, tingling in his extremities, and fatigue came to one of the unit staff through referral from his wife's employer, a professor of Judaica. His symptoms had gradually worsened over several years. The question, "What is your job?" elicited the answer that he worked as a firearms tester in the national ballistics range for the police. His work conditions included exposures to lead-containing dust, fumes, and solvents in a poorly ventilated

firing range without proper exhausts. The level of blood lead was found to be 49.5 $\mu\text{g/dL}$ —a level compatible with toxicity. He also suffered from high blood pressure and ulcers. His wife and two children (f, 15 and m, 13) had blood lead levels of 15.3, 11.5, and 18.0 $\mu\text{g/dL}$ respectively (Center for Disease Control recommended threshold for children: 10 $\mu\text{g/dL}$) (16) most probably resulting from his wearing his contaminated workclothes home. Five years following the discovery of his high level of lead in blood he returned to work at a firing range and he underwent an appendectomy for a complaint resembling acute abdomen. The appendix was found to be uninflamed. Because of personality changes—possibly aggravated by the neurotoxic effects of lead—he was forced into early retirement and loss of full pension rights.

This sentinel individual's story contains an additional lesson: the importance of searching for household exposures to toxic agents from contaminated clothes brought home from the worksite (17). The exposures of the children, though not associated with symptoms, exceeded thresholds for impairing mental function, school performance, and mood status. Thus, the family of the sentinel patient, who had classic signs and symptoms of lead poisoning, had asymptomatic toxic exposures detectable only if actively searched for.

Here, the medical system failed twice to recognize the relation of his abdominal complaints to his lead exposure. The only consolation, for this patient, is that his story belatedly triggered quaternary prevention: a survey of governmental and private firing ranges based on the lessons of his story.

Case 2. Where Do You Work? Dyspnea in a Secretary. A 47-year-old woman, a nonsmoker who had had a runny nose, cough, wheezing, and shortness of breath for several years, came to the Hadassah Hospital Chest Clinic reporting that she was unable to climb more than one flight of stairs. Her condition was one of progressive deterioration despite bronchodilators, antihistamines, and occasional steroid treatment. Chest examination indicated diminished breath sounds and generalized ronchi. A chest x-ray was unremarkable, but pulmonary function tests indicated both obstructive and restrictive impairments.

From questions about her work and what she did, we learned that she worked as a secretary-clerk in a desk job. In this patient, the clue to exposure came from the question, Where do you work? Her job was at the Jerusalem flour mill, where there was massive contamination of her office and the surrounding premises with organic dusts—flour, wheat, soybeans, grain kernels,

and, in wet weather, molds. These are recognized sensitizers of both the conducting airways and, in the latter contaminant, the alveoli (18,19). Removal from exposure based on this question came 8 years after the onset of exposure.

The question, Were there others exposed? elicited the finding that other workers also suffered similar complaints and that turnover of workers was high—often a hint of voluntary self-removal from exposure. Residents living on the street next to the mill had been reporting similar complaints for years from exposure to flour dust blown into their apartments.

A follow-up walk-through site visit elicited information about an additional exposure-effect relationship: rhinorrhea, accompanied by headache, dizziness, and nausea, in her and others, following visits by the pesticide exterminator, who sprayed organophosphates. These agents are recognized triggers of cholinergic responses in the airways through their inhibitory effect on cholinesterase and may have worsened her respiratory status (20).

For this woman, doctors asked for information about her exposures years after the exposures produced illness, and she remained a pulmonary cripple despite her removal from exposure. All that remained to do was to fight for compensation.

If the question “where?” elicits the answer, “shipyards,” past exposure to asbestos has to be considered.

Case 3. What Do You Do? What Are Your Exposures? Sore Throats and Colds in a Worker Exposed to Hydrazine. We have previously reported residual impairments in concentration, comprehension, memory, task performance, and mood status in a 38-year-old water technician whose work involved adding hydrazine, an antioxidant, to the water supply of the hospital in which he worked (21). Hydrazine is readily absorbed via the mucous membranes, the gastrointestinal tract, and the airways, and is a strong irritant and sensitizer. A DNA poison, it has been shown to be carcinogenic, mutagenic, embryotoxic, teratogenic, nephrotoxic, cytotoxic to formed elements in the blood, and neurotoxic in animals.

The technician's problems began with repeated visits to his hospital personnel physician for sore throats, colds, and eye irritation—later recalled to be worse during work hours—treated with erythromycin. During the same period, his wife noticed that he had difficulties remembering things she asked him to do as well as in carrying out household repairs. He also became impotent.

At work, he experienced difficulties in carrying out complex maintenance tasks that he previously performed effortlessly. A psychiatrist to whom he was referred told him he was not mentally ill.

Following his last course of treatment with erythromycin, he developed thrombocytopenia (thrombocytes larger than normal on smear, and a bone marrow aspiration showing an increase in megakaryocytes) consistent with peripheral autoimmune damage. He recovered following treatment with steroids and returned to work, and re-experienced frequent colds and malaise. His difficulties with memory and concentration persisted, and he was unable to perform repair tasks, hold a job in maintenance and repair, or remember material he read in books and encyclopedias. Four years later, he was found to have residual signs of impairment in performance IQ, and moderate impairment of verbal immediate and delayed memory and figure memory.

The patient's sore throats, cough, and eye and skin irritation were the classic local warning signs of the irritative effects of hydrazine. His job title—water technician—gave no hint of this situation. Here, his description of what he did and what agents he was exposed to were the key pieces of information in tracing the work-relatedness of his illness. He poured hydrazine from a tank into a pail. He recalled a constant ammoniac odor, itself an indication of toxic exposure levels. His clothing was frequently soaked, and he would become nauseated and cough when pouring the hydrazine mixture. Here, exposure was not measured, but reconstructed from the description of what he did, smelled, was splashed with, and felt.

The physician's failure to ask the five questions before and after hospitalization forfeited the opportunity to act to stop this man's exposures before the onset of mental impairment. But this episode did trigger quaternary prevention: a parliamentary inquiry into the nationwide lapses in hazard control, worker protection, right to know, and medical awareness of the warning signs of hydrazine exposure in an easy-to-miss set of circumstances.

Case 4. What Are Your Exposures? One Worker, Many Exposures. A 35-year-old worker at a company manufacturing brominated hydrocarbons suffering from severe back and loin pain was referred to the unit by the Department of Nephrology in 1993 for evaluation for end-stage renal disease. At the time of diagnosis, he was excreting 15 gm/L albumin per day (normal: <150 mg/24h). His BUN was 56 mg dL⁻¹ (normal: 10–37), creatinine 2.4 mg/dL (normal 0.6–1.2

g/dL), total protein 5.9 (6.5–8.1), cholesterol 322 mg/dL (120–240), and SGOT 65 μ /mL (5–34). He began working at the chemical plant, which is in the Negev, in 1981. Over the years, he began experiencing throat and chest burning, headache, dizziness, and skin burns following air and skin exposures to aromatic vapors, gasses, and liquids at this work site. He suffered from pitting edema, shortness of breath, ascites; he requires dialysis, and he is a candidate for a transplant. He and his brother both had prior deep vein thrombosis.

His day-to-day exposures to many agents (Table 1) resulted from wading through flooded drainage canals and puddles and inhalation of vapors. A past exposure to ethylene and methylene chloride—which can produce carbon monoxide intoxication through its metabolic breakdown products—resulted in loss of consciousness. Another time, he and five other workers were hospitalized for burns from monobromoacetic acid. Six (40%) of 15 workers in his unit (age range, 30–50) have epilepsy, hepatic and renal disease, and facial nerve paralysis, and one died from lung cancer at age 52. He was never told about his toxic risks, acute or chronic, from his exposures.

In this patient, years elapsed not only between both the onset of exposure and his renal disease, but also between the latter and when medical search for exposures was initiated. The target organ systems for the impairment from solvents are fat-soluble organs—central and peripheral nervous system, liver and kidneys and placenta. Usually, the central nervous system (CNS)

TABLE 1
Sentinel Chemical Worker: Self-Reported Exposures

Minerals and Metals	
Aluminum tribromide	Brome
Aluminum dust	
Organic Compounds	
Alpha bromopropionic acid	Ethylene glycol
Benzene	Methanol
Bromochlorodimethylhydantoin	Methyl bromide
Butane diol	Methylene chloride
Decabromodiphenyloxide	Monobromoacetic acid
Diphenylether	Phenol
Dibromocyanoacetamide	Tetrabromoethane
Dibromomethane	Tetrabromoxylene
Ethylene dibromide	Toluene
Ethylene dichloride	
Acids, Bases, and Salts	
Aluminum chloride	Phosphoric acid
Ammonia	Hydrobromic acid
Sodium and potassium bromate	Boric acid
Sodium dichromate	Acetic anhydride acid
Citric acid	Sodium bicarbonate
Sulfuric acid	Sodium bisulfate
Hydrochloric acid	

is the first and most vulnerable target organ system, and the first symptoms in sentinel patients may be headache, dizziness, mild nausea, and, often, short-term memory problems, usually reversible with early termination of exposure. As years go by and exposure continues, other effects, including parenchymal changes in liver and, later on, the kidney, may emerge. The plausibility of this individual's renal disease being related to his exposures is suggested by case-control studies describing the association (22). The later the intervention, the less the sentinel patient could be helped. Furthermore, others in the same work environment were reported to have illnesses plausibly associated with solvent exposure.

CNS complaints tend not to be accompanied by "hard" neurologic findings, and detailed questioning or neurobehavioral testing is needed to discover impairment (23). An independent study, recently completed, showed associations between bromine levels and various measures of neurobehavioral impairment based on examinations of over 400 workers from the factory in which this worker was employed (Michal Eldan, personal correspondence).

Retroactive attempts to approximate past exposures, based on what the patient told us, had to be qualitative. Many agents were involved, skin as well as airway were the absorption routes, and temporal patterns were episodic or sporadic. This patient's susceptibility to exposure may have been increased by an unrelated and poorly understood familial problem, deep vein thrombosis.

The exposures to mixed solvents that occurred here may have later increased risks for cancer. The occurrence of lung cancer may be re-

garded as a possible sentinel event for these risks, although brain, blood, renal, and hepatic tumors are the "signal" events (24). But the noncarcinogenic events appear earlier, are more widespread, and result from exposure levels higher than those needed to increase risk for cancer (25). Therefore, the prevention of noncarcinogenic effects should help to remove carcinogenic risks.

Case 5. When Are Your Symptoms Worse? Headache, Insomnia, and Flulike Illness in a Family. A mother, her two children, and the family housekeeper reported a variety of complaints (Table 2) for a period of 4 1/2 months (26). A family physician finally asked, "When did the symptoms appear or become worse?" The answer: the flulike complaints first appeared after the family entered their new apartment, and following the visit of the exterminator, who sprayed diazinon, an organophosphate. The housekeeper felt ill only after coming to the family home.

The findings triggered the search for proof of exposure, as measured by urine alkyl phosphate metabolites and depressed whole blood cholinesterase. We found an open bottle of diazinon left behind in one of the clothing closets, and contaminated clothing and wall panels in the apartment. After decontamination, urine metabolite levels dropped to below the threshold of detection, cholinesterase levels rose, and the patients all became asymptomatic.

The investigation of this index sentinel family triggered another exercise in quaternary prevention: the search for and discovery of other contaminated households with ill individuals treated by the same company.

With colleagues, we have shown that flulike

TABLE 2
Serum Cholinesterase (ChE) and Diethyl Phosphate (DEP) Levels in One Family Before and After Clean-up

Subject (age)	Complaints	Before clean-up 3/15-16/89		After clean-up 5/7/89 8/7/90	
		DEP (mg/L)	ChE (IU/L)	DEP (mg/L)	ChE (IU/L)
Mother (30 y)	Fatigue Sleep problems Irritability	0.45	5.3 (-11.7%)*	<.01	6.00
Father (35 y)	—	1.70	6.5	<0.1	—
Daughter (4 y 6 mo)	Vomiting	0.77	6.2 (-21.6%)*	<.01	7.9
Daughter (1 y 2 mo)	Vomiting Runny nose	1.27	7.4 (-6.4%)*	<.01	7.9
Housekeeper (35 y)	Dizziness Headache Chest heaviness	—	—	—	—

* Depression measured against post-clean-up baseline (8/7/90).

illness and gastrointestinal complaints in Israeli kibbutz residents, as well as cotton field workers, were directly associated with exposure to organophosphate-containing pesticide drift, demonstrated by alkyl phosphate metabolite levels in the urine (27).

Case 6. Are There Others? Many Workers, Many Exposures. The Unit of Occupational and Environmental Medicine investigated (28) an epidemic for which the sentinel event was the death, in 1987, of a 48-year-old male worker from what was diagnosed as an atypical "amyotrophic lateral sclerosis-like syndrome" after his widow came to us. This patient suffered from muscle pain, severe headaches, cough, and bloody sputum, as well as motor nerve paralysis; the history of pain raised questions about the validity of the diagnosis.

The sentinel patient was employed in a plant that manufactured nickel-cadmium batteries. A colleague on the same assembly line died shortly thereafter of end-stage renal disease and was reported by his colleagues to have suffered from the same set of problems. Thereafter, a 49-year-old woman from the same factory who had hairy cell leukemia came to us at the unit, and we were advised of the deaths of two males, one who died at age 58 from lung cancer after suffering from chest pain and loss of sense of smell for two years, and another who died at age 51 from pancreatic cancer. We asked, Were there others? Following a meeting with the workers, 38 (21 women, 17 men; age range, 31–63; duration of employment, 2–20 years) came to us at the unit for medical evaluation. Thirty-four worked on the nickel-cadmium battery assembly line. Symptoms were headache in 34; weakness, fatigue, and lassitude in 26; dizziness in 16; pruritus and skin eruptions in 37; gingivitis, teeth loss and caries in 34; nasal congestion, nosebleeds, and anosmia in 30; cough, phlegm, wheezing, and shortness of breath in 26; "asthma" in 14; bone pain in 18; urinary frequency, B₂ microglobulinuria, and kidney stones in 17; and sterility and 33 multiple abortions in 8 of 21 women. CT scans in six workers were reported as describing brain atrophy. Those who had worked for more than 10 years had more symptoms and signs—especially neurological illness, bone pain, and renal problems—than those who worked for fewer years (Table 3).

Past cadmium levels were in the range of 1.6–8.7 µg/dL in blood and 8–306 µg/dL in urine, much higher than background population levels and above the WHO "action" level (0.5 µg/dL) for preventing renal disease, the critical effect from cadmium. Other than cadmium and nickel, there

TABLE 3
*Selected Complaints and Findings by Exposure Duration in Nickel-Cadmium Battery Workers**

Complaints	Length of employment				Odds ratio A/B
	≥10 yr (n = 22) A		<10 yr (n = 12) B		
	No.	%	No.	%	
Neurologic Headache, dizziness, fatigue, brain atrophy	22	100	12	100	1.0
Dental-oral Bleeding gums, caries, teeth loss	22	100	12	100	1.0
Skin Itching, sores	22	100	11	91	1.1
Nasal Nosebleeds, congestion, loss of smell	20	90	10	83	1.1
Bronchopulmonary (shortness of breath, cough, phlegm, wheezing)	20	90	6	50	1.8
Bone pain	18	81	0	0	>2.7
Urogenital Urinary frequency, kidney stones, B ₂ -microglobulinuria	17	77	0	0	>2.9
Spontaneous abortions [†]		3	8/21	38	

* Employed in nickel-cadmium assembly line only.

† 33 abortions in 8 women, 3 women permanently sterile.

were exposures to many other raw materials, intermediate processes, and reagents. A list of agents used and exposures in the battery plant was obtained from histories, inspectorate reports, and depositions (Table 4). Our investigation indicated that health risks for workers were not confined to the nickel-cadmium assembly line or to older workers, and that hazardous exposures persisted and illness appeared in new workers after a clean-up and intervention program. Based on exposure-effect data from cadmium alone, the workers with exposure to this agent were at substantially increased risk for late renal disease—the critical effect (that outcome which, if prevented, will result in prevention of all other effects).

Later, well water in the vicinity of the factory

TABLE 4
Agents Used in Nickel-Cadmium Battery Plant

Metals	Nickel, cadmium, lithium, cobalt, chromates, manganese, magnesium, silver, zinc
Glues	Epoxies, cyanoacrylates, acrylonitrile-butadiene-styrene
Solvents	Freons, acetone, alcohols
Bases	NaOH
Acids	Sulfuric, nitrous
Other	Asbestos-based dusts and powders

was shown to be contaminated by cadmium, and it is possible that an earlier report of an unexplained high incidence of wheezing in children in neighboring homes is attributable to airborne drift from debris dumped in and around the factory grounds (29).

The patients were the tip of an epidemiologic iceberg. The true population-at-risk is now considered to be more than 1000 persons ever employed. For more than a decade, the exposure-outcome associations were missed, despite abundant evidence that patients went to their physicians, were interviewed, examined, and treated for their complaints. This industrial disaster was a consequence of the systematic failure of the medical care system to search for the work-relatedness of not one, but many sentinel patients subject to many exposures.

Case 6. What Went Wrong? This story documented an array of systematic failures of the entire medical care system:

- Physicians and dentists confined their attention to the single organ system associated with the initial complaint in each patient and failed to search for circumstantial associations. Itching was treated with antipruritics, airway obstruction with bronchodilators and steroids; neurologic problems with painkillers, sedatives, and tranquilizers, and dental problems received prosthetic dental work. Occupational histories were not taken, and longer term risks—renal disease, cancer—were not considered. Women who spontaneously aborted were sent back to their workplace exposures, counseled, or given hormones.
- Each physician confined his attention to a single patient, without asking whether there were others. This precluded recognizing that each person's sentinel event signaled an epidemic, that is, a condition or group of related conditions found to occur in a population at greater than expected rates.
- Physicians neglected the importance of exposures to agents other than those associated with the final products, nickel-cadmium batteries.
- Physicians used unsafe bureaucratic standards, not health-based toxicologic long-term data on subacute exposures, to assess risk. Even after there was recognition that the factory contained sites of many hazardous exposures, workers were told to return to work after recovery from acute illness. Unsafe bureaucratic standards led to the persistence of hazard and risk after the clean-up.

New Trends

My Eyes, Back, Wrist, and Neck Hurt. Do You Work on the Computer? Punching the keyboard and looking at the video display unit are what ever-increasing numbers of the workforce spend more and more hours doing. The environment is clean, but produces hazardous ergonomic exposures. Vision accommodation problems, eye strain (30), carpal tunnel syndromes, shoulder and hand problems, and repetitive trauma syndromes are sentinel events (31) reflecting the transformation of work brought by computerization. The unit sees patients with these problems who undergo costly diagnostic studies that do not include a history or evaluation of these ergonomic exposures. Musculoskeletal problems, including eye strain from accommodation difficulties, cannot be evaluated without recognition of the pervasive impact of the ergonomics of typing and looking at the video display unit. Also, possibly increased risk of spontaneous abortion from first trimester work with video displays and exposure to ELF electromagnetic radiation are issues of concern (32).

Are You Happy in Your Work? Stress in the Workplace and Smoking. Fear of job loss, lack of communication between peers and with superiors, blocks to promotion and job uncertainty, and lack of job satisfaction have been shown to be predictors of increased diastolic blood pressure (33). These are definable work stressors. Furthermore, the role of these and other stressors in increasing risks for smoking—which itself increases risks from other exposures—is well recognized (34). Smoking rates are higher in precisely those groups exposed to other toxic hazards (35). In working women, the rising incidence of smoking since the 1980s (36) suggests a need to examine the role of workplace stressors in this trend.

Smoking, active and passive, remains one of the top-ranking causes of cancer and lung and heart disease in most parts of the world (37). It does not account for all risks from pulmonary, cardiovascular, and carcinogenic events associated with combined exposures (38); it exacerbates their effects through well-recognized mechanisms (39).

There is a precautionary message concerning efforts to promote smoking cessation: success, especially in the workplace, hinges on parallel efforts to reduce other workplace exposures (40). Shift work, incentive premiums, tethered work, and working in subcontracted settings are sociopsychological environments in which risks for stress, and in fact for the older toxic and physical

Unit of Occupational and Environmental Medicine
Hebrew University-Hadassah School of Community Medicine and
Public Health, Jerusalem

Are there hazards for injury and toxic exposure at your worksite?
Checklist for the Walk-Through Site Survey

Workplace records and organization
(Who, When, Where, Which, What, How)

	frequency	severity	duration	location	shift/hour
absenteeism					
injuries					
illnesses					

Plant design/layout

process flow charts

operations

distribution of process equipment

material flow: transport, use and disposal

location/type engineering controls

dimensions (including ceiling heights)

ventilation and exhaust systems

Structure and presence of hazard control program

log of agents and haz-mat classification

material data safety sheets: use and clarity

labelling: clear and user friendly?

use of safety equipment: safety shoes,

safety clothing, hard hats, goggles, ear

protection, respirator protection

equipment, whole face protectors

respirators: use, appropriateness,

adequacy, and maintenance

control over subcontractors

work conditions of shift workers

Suspicion of *workplace hazard or worker risk* when the following occur or are observed:

eye irritation when *entering or remaining*

odor

metallic taste

visible clouds of dust on operation

noise level requires voice to be raised

exhaust/vent systems are not capturing all

contaminant or escaping contaminant is

diffusing into workplace

visible fumes are released into the workplace

e.g. welding/without local exhaust

unlabelled bottles, containers

spills, puddles, careless handling of toxic materials

substances which are hazardous stored at site

e.g., carcinogens and toxics are kept

under open storage/uncapped bottles

absence of closets for separate enclosed storage of

chemicals

excess heat or cold

intense light without eye protection

e.g. gas welding and flame cutting

body vibration

signs of skin or clothing contamination

poor housekeeping

eating place not separate

absence of clean toilet and facilities for washing,

showering, and changing clothes

young children or teenage workers

worker comments about symptoms, e.g. headache, fatigue, dizziness, nausea, breathing difficulties, skin problems or high turnover/dropout

hazards as well, have not been adequately recognized.

The Walk-Through Site Survey

The sensitivity and specificity of the trigger questions are augmented by expanded checklists and by what is known as the walk-through site survey. Such surveys offer an opportunity to directly determine whether the individual patient's sentinel event is part of a larger picture. Because walk-throughs are not a part of the conventional doctor-patient encounter, we underestimate their effectiveness. The unit has developed a checklist for the walk-through survey (see box).

The Macro-Environment

Death from all cancers combined has failed to decline in modern Western societies (41). Improvements in palliative therapy have been offset by rising incidence, especially in blood, brain, skin, prostate, and breast cancer (42). These trends have called attention to preventable "macro" environmental and nutritional determinants of illness outside the scope of medical care, including community and home air pollution, fat content in diet, pesticides, solvents, hormones, and ionizing and nonionizing radiation. But changes in environment outside the scope of medical care, lifestyle, smoking and nutrition are now part of the agenda for health promotion in routine management not only of patients, including those who have undergone events, but also of populations, and recall the recommendation of Bernard Shaw that doctors, internists included, should be paid to keep people healthy.

New Approaches to Searching for and Preventing Exposures

Empowerment of sentinel patients to help them modify their work environment has been suggested to be the emerging agenda in worker and community health (43). In an era when doctor-patient relationships are interactive, not paternalistic, the physician's role will be to catalyze retrieval, interpretation, and effective use of information. Patients treated in the unit, especially those who are self-referred, are making use of right-to-know laws and regulations computerized on-line information services. We teach them to use key words for suspected agents (for example, toluene) or class of agents (e.g. aromatic solvents), job settings (e.g. lab workers), and outcomes (e.g. short-term memory loss, headache, fa-

tigue; Hodgkin's disease) to carry out their own customized searches for information based on job-exposure matrixes and material data safety sheets. The role of the physician is already changing from one of provider of information on exposure-effect relationships to consultant, interpreter, and guide.

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Authors' note added in proof:

Patient no. 4 was killed in a road crash in August 1995. He was driving. No studies are available on road-crash risks in drivers who have undergone neurotoxic exposure to agents other than alcohol in the workplace (personal communication from A. Fischbein).

Medical and Public Health Approaches to Asbestos Disease

ARTHUR L. FRANK, M.D., PH.D.

Abstract

Asbestos is known to cause a wide range of nonmalignant and malignant disease among occupationally and environmentally exposed individuals. Lung cancer and mesothelioma are of special importance. X-rays are evaluated utilizing the ILO classification, and the clinical signs and symptoms of many chronic lung diseases may occur. The fibrous nature of asbestos appears to be important, and fiber size plays a role in carcinogenic outcome.

Because of the significant legal and public health implications of exposure, it appears that purposeful obfuscation of asbestos science has taken place. There are also worldwide efforts to shift patterns of use and manufacturing, leading to a wider dissemination of death and disease, especially when coupled with spreading tobacco usage.

If I am not for myself, who will be for me?
And if I am only for myself, what am I? And
if not now, when?

Hillel, *Pirke Aboth*

I COULDN'T BUY the house I wanted recently. The reason may strike some as making little sense, but it is a classic example of the clash of personal and societal needs and in my case, looking at the world through the eyes of a public health physician; the societal issue won out. Having recently accepted a new academic position, I needed to find a new home for my family. The one that we found that would suit us unfortunately was found to contain considerable amounts of asbestos. The owner, unaware that such a situation even existed, was reluctant to meet my contractual requirement to remove all the asbestos from the house as a condition of sale. I would have enjoyed living in that house. My search, and testing, continued.

Although it is not much in dispute any longer

that asbestos causes considerable disease and death, much controversy continues on the public health approach to this material. The diseases caused by asbestos are now well appreciated, but mechanisms remain elusive.

The Pneumoconioses

The pneumoconioses, or dust diseases of the lung, first described by Zenker in the last century, have been appreciated for millennia (1). Workers in mines, the knife-grinders of Sheffield, and construction workers in this century have all shared similar fates. The list of pneumoconiosis-producing dust is long (Table 1) and although the basic pathologic and clinical changes that follow exposure are similar, several of the dusts have special related problems. For example, for reasons not well appreciated, exposure to silica carries with it the special problem of tuberculosis, described in the past as the condition of silicotuberculosis, an appellation given to no other dust disease of the lung. Asbestos has the ominous distinction of association with a variety of malignancies that occurs with no other dust exposure, for reasons not well understood. As if science, in and of itself, was not difficult enough, some have chosen to further obfuscate and intermingle questions of science and matters of economics. As Dr. Irving J. Selikoff, the physician most often asso-

From the Department of Medical Education, University of Texas Health Center, Tyler, TX. Address reprint requests to the author, Topperman Professor of Medicine, Associate Director for Medical Education, Department of Medical Education, University of Texas Health Center, P.O. Box 20003, Tyler, TX 75710.

TABLE 1

Selected Etiologic Agents Causing Pneumoconiosis

Agent	Disease
Coal	Coal-workers pneumoconiosis (CWP)
Silica	Silicosis
Asbestos	Asbestosis
Talc	Talcosis
Kaolin	Kaolinosis
Fuller's earth	
Mica	
Graphite	
Zeolites	
Aluminum	Aluminosis
Beryllium	Beryllium disease
Hematite/iron	Siderosis
Tin	Stannosis
Titanium	

ciated with the study of asbestos-related disease, often stated, "Where money changes hands, there one can find difficulty" (personal communication; 2).

The pathologic changes associated with the pneumoconioses are relatively simple and straightforward. Exposure to dust leads to phagocytic activity of macrophages, which in turn leads to tissue reactions resulting in the production of collagen-based connective tissue in such a way as to inhibit the transfer of oxygen at the level of the alveolus, and which can be seen radiologically as rounded or irregular opacities, and in the case of some dusts, can affect the pleura as well, leading to thickening or calcification. The pleural changes are also characterized by a deposition of collagen, mirroring the process in the lung parenchyma.

Clinically, the pneumoconioses are characterized by shortness of breath and occasionally an irregular cough, and laboratory testing may document abnormal results on chest x-rays and CT scans, pathologic changes in tissues seen with light or electron microscopy, and pulmonary function abnormalities traditionally thought of as restrictive, but there is a growing body of evidence that obstructive changes occur as well (3). Not surprisingly, there are also important interactions related to the smoking habits of individuals exposed to dust, with sometimes ominous implications.

Asbestosis

Asbestos disease was appreciated by the ancients and was regularly commented on in the scientific literature of Western medicine starting at the beginning of the 20th century. The risk of

TABLE 2

Asbestos-Related Diseases

Nonmalignant	Malignant
Asbestos warts	Lung
Benign asbestotic pleural effusion	Mesothelioma
Asbestosis	Pleural
Parenchyma	Peritoneal
Pleura	Pericardial
	Gastrointestinal
	Esophagus
	Stomach
	Colon/rectum
	Kidney
	Laryngeal/oropharyngeal

individuals exposed to asbestos was first appreciated in the scientific literature around 1900, and a major insurance industry company in North America ceased writing policies on the lives of some asbestos-exposed workers as early as 1918. As is true for the progress of most scientific issues, there have been, and continue to be, increasing numbers of papers devoted to various aspects of asbestos-related disease, the most recent trend being toward mechanistic papers at the cellular and genetic level.

Definitions of Asbestosis and Scientific Accuracy. As noted above, asbestos causes both non-malignant and malignant diseases (Table 2). Asbestos incontrovertibly causes asbestosis, but the definition of that term varies among scientists. What is ironic, however, is the now well documented approach of revisionists who seem to serve a wider range of needs than clinical medicine or true scientific investigation. Arguments are bent back and forth to serve particular needs and settings, rather than being aimed at scientific accuracy or consistency.

Pathologic Change in Lung and Pleura. For some, the term asbestosis applies only to pathologic changes in the lung parenchyma and not to alterations in the pleura. I find at least three different grounds on which to disagree with this view. First, the original description of the pneumoconioses by Zenker specifically included changes in the pleura that he noted in a worker he described in his original paper. The disease, in that case, was not caused by asbestos, but the term pneumoconiosis was applied to both parenchymal and pleural changes. Secondly, as noted above, the cellular activity in terms of pathologic change in both the parenchyma and pleura are identical, a deposition of collagen with the resulting fibrosis.

Lastly, the widely adopted standardized international classification for the reading of

x-rays, the ILO classification, which has been utilized in one form or another for some fifty years, asks if there are pleural changes consistent with pneumoconiosis, recognizing that some of the dusts can evoke pleural change. For some years now, there has been a movement to try to "define away" asbestosis as applying to pleural changes, and the finding of fibrotic lesions in the pleura has been looked on, by some, as not being evidence of disease, but rather as a "marker" or calling card, or dismissed as some insignificant aspect of exposure. Ironically, recently, in a legal context, it has been argued that fibrotic changes in the lung of a patient were thought not to be asbestosis because there were no pleural changes to go along with parenchymal changes, invoking such changes as central to the definition of the disease entity.

Clinical Signs. The clinical signs that may, but relatively rarely do, accompany the pneumoconioses, including asbestosis, include the finding of dry rales, clubbing, cyanosis, and, in advanced cases, the usual stigmata of advanced pulmonary disease. Somewhat inexplicably, there are those who require evidence of such clinical changes to make the diagnosis of asbestosis, although this situation does not apply to other diagnoses that are similar; for some disorders, for example, x-ray changes alone can suggest a diagnosis which is confirmable with further laboratory testing—evidence of a Ghon complex can lead to a diagnosis of tuberculosis, egg shell calcifications of hilar nodes can lead to a diagnosis of silicosis, and calcified granulomas, can lead to the diagnosis of histoplasmosis in appropriate parts of the country. In none of these cases would documentable clinical changes be required, as some seem to require for a diagnosis of asbestosis. Some have even gone so far as to require specific pulmonary function changes as well.

The ILO classification utilized to evaluate x-rays was not designed as a tool for clinicians, but as a tool for epidemiologists interested in the public health aspects of asbestos-related disease and other population-based issues regarding the wide range of pneumoconioses. In fact, the use of this classification specifically does not allow for a diagnosis to be made, but only for an x-ray to be described, in terms that can then be understood by any other individual familiar with the classification system, even without, necessarily, seeing a specific x-ray. Regrettably, what has happened to an excellent tool for the epidemiologist has been thrust into the legal world of asbestos-related liability, a purpose for which it was never intended.

Definitive Diagnosis. For this author, and for many other physicians, the ability to make the diagnosis of asbestosis rests on no more than two pieces of information;

- first, and obviously essential, significant documented exposure to asbestos to allow a diagnosis of asbestosis, from either occupational or environmental sources
- second, some evidence of abnormality which, when coupled with the history of exposure, can lead to a diagnosis. The most commonly available piece of information is the chest x-ray; certain characteristic changes, in light of significant exposure to asbestos, can support a diagnosis of asbestosis, in both parenchyma and pleura. Rarely available, but equally good, if not better, is tissue from an exposed individual showing characteristic changes of fibrosis on microscopic examination

"Significant" Exposure, Thresholds, and Malignancy. Exposure to asbestos can occur, and regularly does occur, to almost every individual, especially in industrialized societies. Asbestos, after all, is a group of naturally occurring fibrous silicates, the use of which has been exploited by humans, particularly in the 20th century.

The term "asbestos" refers to a family of six fibers, divided into two groups, the amphiboles (amosite, anthophyllite, crocidolite, tremolite and actinolite), and the one serpentine form, (chrysotile). There are structural differences between the amphiboles and the serpentine form, but all asbestos types, and only four are commercially viable, are fibrous in nature, and it is thought that their fibrous structure carries with it the significant malignant risk. As is made clear below, although virtually everyone may have some exposure to asbestos, the clear threshold effect for the development of asbestosis precludes rational consideration of most individuals as at risk for asbestosis.

However, a malignant risk is altogether a different matter. All of the fiber types of asbestos have been related to the development of malignancies in humans or experimental animals (4–7). Asbestos has been generally recognized—except by a few individuals generally thought of as outside the mainstream of science—as causing lung cancer and mesothelioma. Other malignancies have also been related to asbestos exposure, although with more controversy and less general agreement on certain malignancies. The generally accepted view, and the regulatory point of view adopted in the United States, recognizes an

excess of gastrointestinal tract cancers, renal cancers, and laryngeal cancers as being associated with asbestos exposure. Some cancers, such as ovarian cancers among women, have been suggested to be related to exposure, but because of the relative paucity of women exposed in the past, at least in traditionally studied countries, this is a matter as yet undecided.

The cell types of lung cancer associated with exposure to asbestos are the same as those that occur in the general population of lung cancer patients, where cigarette smoking is the predominant causative factor (8, 9). What is somewhat different is that a greater proportion of cases are found in the periphery of the lower lung zones, the same areas most commonly affected by asbestosis, rather than the more usual upper lobe, central location. An area of significant research is the question of fiber size, well documented by Stanton with regard to the development of mesotheliomas (10).

There have been various models of malignant disease with regard to exposure to asbestos, but whatever the suggestions of possible relationship, it is clear that exposure to asbestos and to asbestos alone can produce lung cancers, mesotheliomas, and other malignancies discussed above.

Synergism of Smoking and Asbestos. However, smoking interacts significantly with asbestosis in some diseases. In fact, almost thirty years ago Selikoff and colleagues (11) first brought to the world's attention the synergistic malignant potential of asbestos and cigarette smoking. Other synergistic relationships that have been documented in the scientific literature are exposure to radiation among miners who also smoke, leading to an excess of lung cancers, and the concomitant exposure to certain industrial chemicals, like benzene, and excessive use of alcohol, leading to enhanced bone marrow depression.

Modern carcinogenesis theory documents that there is no "threshold" for exposure to carcinogens below which a malignancy is not possible. Although virtually impossible to document scientifically at the present time, the concept that one molecule of a carcinogen, or one fiber of asbestos, could have the potential for inducing cancer is one that is tenable. This is obviously a somewhat simplistic view, as well, since a multitude of factors lead to the development or nondevelopment of malignancies in any individual, including genetics, host factors, and immunologic status. Nevertheless, the basic principle is that even small amounts of exposure carry some risk, although the risk is clearly related to how much exposure takes place. The classic dose-response

TABLE 3
Selected Occupations Shown to Be Associated with Asbestos-Related Disease

Miners and millers	Railroad workers
Insulators	Shipyard workers
Textile workers	Custodial workers
Construction workers	Telephone installers
Plumbers/pipefitters	Steelworkers
Electricians	Cement workers
Sheetmetal	Maintenance workers
Painters	Seamen
Elevator installers	Jewelers
Others	Powerhouse workers
Auto mechanics	Refinery workers

Significant environmental exposure occurs in those living near mines, factories, and shipyards and in family members of workers.

principle, which applies to so much of biology, clearly applies here as well.

Having recognized that the risk for cancer occurs at levels below which one would not expect to see evidence of asbestosis has led to the realization that in virtually every occupational population in which asbestos disease has been looked for, it has been found (Table 3).

Contribution of Environmental Exposure. There is also another aspect of exposure to asbestos, in that it is not a respecter of workplace or job category, and environmental disease can occur as well as disease specifically linked to employment. Wives and children of asbestos workers have developed asbestos-related diseases, as have individuals in populations living near facilities utilizing asbestos.

The issue of threshold vs. nonthreshold exposure for nonmalignant and malignant disease has been, it appears purposefully, muddled. Some claim that for a cancer to be linked to asbestos, evidence of asbestosis is necessary. There are clearly many reasons why this is not accurate, but again, this view has been widely put forth in some settings for other than scientific reasons.

One of the significant medical and public health issues related to asbestos exposure is the importance of a full and accurate occupational history, something few physicians have been well trained to do, or to do regularly (12). Environmental exposures are even less well appreciated. The lack of adequate historical assessment may lead to misdiagnosis, or to lack of recognition of the workplace origin of disease, depriving workers or their families of just compensation either through the traditional workers compensation mechanism or through third-party suits against the suppliers of asbestos who had knowledge of disease for many decades (13).

Scientific Revisionism and Legal Activity. It is this author's view that much of the revisionism and inaccuracy with regard to asbestos-related information (14, 15) has been the result of legal activity. The inaccuracy of the literature, sometimes even contradicting a scientist's own previous work, is clearly puzzling. The puzzle becomes clearer when one realizes that, by EPA estimates, some 700,000 public buildings in the United States have asbestos in them, and many dollars are at stake in the question of who should pay for its removal, which clearly should be done.

Future Epidemics. Perhaps, as we close out the 20th century, the most disheartening aspect of issues regarding asbestos is that as industrialized countries decrease or ban its use, manufacturing facilities are being established in developing nations to shift the risk of disease. This has been coupled with aggressive marketing of another hazardous product, tobacco, and we now face the development of disease in a predictable fashion throughout the world (16).

One should remember that asbestos-related problems are preventable. However, as recently documented again (17), disease will follow us well into the 21st century from asbestos use in the past. This failure of past preventive practices, and the current lack of attention to these lessons, dooms us to future epidemics of disease (18).

Epilogue

One must look after one's own interest, and that of one's family, but not to the exclusion of the societal good. This communal view must be adopted now, not in the future. These sentiments from Hillel's *Pirke Aboth*, "Sayings of the Fathers," apply to what we know about asbestos, as well as to so many other things in life.

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Clinical Recognition of Occupational and Environmental Disease

PHILIP J. LANDRIGAN, M.D., M.Sc., AND DEAN B. BAKER, M.D., M.P.H.

MOST PERSONS spend many years of their lives at work, and the evidence is persuasive that chemicals and processes encountered at work are responsible for many cases of illness (1). It is important therefore that physicians, particularly those engaged in primary care, have a basic understanding of occupational and environmental medicine. Physicians need to be able to recognize and diagnose diseases that are caused or exacerbated by occupational and environmental factors (2). The American College of Physicians has recommended that medical training at every level place increased emphasis on occupational and environmental medicine. Also, the American College of Physicians has recommended that physicians routinely inquire in the diagnostic interview about patients' occupational and environmental exposures (3-4).

Occupational and environmental toxins can cause a broad range of illnesses, and these diseases can involve virtually every organ system in the human body (1). They include classic, well-described diseases such as lung cancer and malignant mesothelioma in workers exposed to asbestos; cancer of the bladder in dye workers; pneumoconiosis in coal miners; leukemia and lymphoma in people exposed to benzene; skin cancer in farmers and sailors chronically exposed to the sun; and chronic bronchitis in workers exposed to dusts. They also include newer entities recognized only in recent years, such as dementia in persons exposed to solvents; sterility in men

and women exposed to certain pesticides; and asthma and bronchitis in children and adults chronically exposed to air pollution. Some of these diseases are acute; others are chronic. Some are manifest through obvious symptoms, while others involve more subtle degrees of dysfunction.

In the United States, occupational exposures account each year for an estimated 50,000 to 70,000 deaths and for 350,000 new cases of illness (5-6). An additional 10 million people suffer traumatic injuries on the job each year, and 10,000 die of occupational trauma. As for environmental exposure, the Centers for Disease Control and Prevention estimates that at least 2 million children suffer from lead poisoning and that tens of thousands have asthma induced by air pollution. Occupational and environmental exposures always need to be considered in formulating a differential diagnosis. Because of the enormous numbers of persons exposed and the wide range of illnesses, occupational and environmental exposures need to be sought in every patient.

Clinical Diagnosis of Occupational and Environmental Disease

Occupational and environmental diseases are underdiagnosed. Many are incorrectly attributed to other causes because frequently these diseases are not distinct in their clinical presentations and can closely resemble chronic diseases caused by other factors (7). Some examples:

- Lung cancer caused by asbestos, radon, or beryllium is commonly attributed to cigarette smoking
- Severe abdominal pain caused by lead poisoning may be erroneously diagnosed as acute appendicitis; such cases have resulted in unnecessary surgery

From the Department of Community Medicine, Mount Sinai School of Medicine, New York, NY (PJL); and the Center for Occupational and Environmental Health, University of California, Irvine, CA (DBB). Address reprint requests to Philip J. Landrigan, M.D., M.Sc., Ethel H. Wise Professor of Community Medicine, Chairman, Department of Community Medicine, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1057, New York, NY 10029-6574.

- Dementia caused by organic solvents has been attributed to "old age" or to ethanol ingestion
- Renal failure caused by chronic exposure to cadmium has been ascribed to "idiopathic factors"

Only if a careful history of toxic occupational and environmental exposures is taken in such cases can a correct diagnosis be made. A barrier to accurate diagnosis is that a long latency interval frequently elapses between occupational or environmental exposure and the appearance of disease. For some occupational and environmental cancers (for instance, mesothelioma caused by asbestos, or lymphoma caused by benzene), this latency may span decades (8). Another impediment to diagnosis is that many people have had multiple toxic exposures at work or in the environment over the course of their lifetime. Also, at least until recently, workers were often not given the names of the materials with which they worked, nor were they provided with adequate information about the hazards of these materials. For these reasons, it is often difficult for the physician to accurately ascertain the nature of a patient's past exposures.

The keys to properly diagnosing occupational and environmental disease are:

- obtaining an adequate history of occupational and environmental exposure for every patient
- possessing basic knowledge about the pathogenesis and clinical presentation of the major types of occupational and environmental disease
- knowing how to report suspect cases of occupational and environmental illness to public health authorities so that additional cases caused by the same exposures can at least be recognized and at best prevented

Physicians should be especially knowledgeable about the occupational and environmental diseases that occur commonly in their geographic practice areas, such as asbestosis and malignant mesothelioma in port cities with shipyards, pesticide intoxication in agricultural areas, and poisonings from solvents and exotic metals in regions that produce microelectronics (9–10).

The Occupational and Environmental History

The history is the single most important instrument for obtaining information on the role of occupational and environmental factors in causing disease (7). Information about current and

past exposures should routinely be sought at several logical points while taking every patient's history. At each juncture, a few brief screening questions need to be asked systematically. Then, if suspicious information is elicited, more detailed follow-up questions are needed. An efficient, routine screen for occupational and environmental disease consists of the following items:

1. In the history of the present illness. Pay attention to any temporal relationship between onset of illness and introduction of toxic exposures in the workplace or the environment. For example, did symptoms begin shortly after the patient started a new job? Did they abate during vacation and then recrudescence after the patient resumed work? Were they related to the introduction of a new chemical or process? Did they correlate with episodes of pollution? Were there similar illnesses among coworkers or neighbors? Were the individuals who were more heavily exposed the more severely affected?

A possible occupational etiology should be sought in every case of acute trauma (in children and adolescents as well as adults, because too many children work at dangerous jobs) and in every case of repetitive trauma, as for example carpal tunnel syndrome.

2. In the past medical history. Obtain a list of current and principal past occupations and of industries of employment. Each patient should be asked whether he or she ever developed illness as a consequence of work.

3. In the review of systems. Routinely ask every patient, "Do you now or have you previously had occupational or environmental exposures to asbestos, lead, fumes, chemicals, dusts, loud noise, radiation, or other toxic factors?" Also ask every patient whether he or she believes that any of these factors may have caused or contributed to his or her illness. Even if a postulated connection between exposure and disease initially appears tenuous, such suspicions always need to be carefully considered.

Detailed Exposure History. If information from the routine interview suggests an occupational and environmental etiology, the physician should obtain a more detailed history of toxic exposures. Duration and intensity of exposures are particularly important. It is necessary to learn how the patient worked with the suspected toxin and to consider how he or she may have absorbed the material; information should be obtained on all jobs ever held, places of employment, products manufactured, and materials with which the patient worked (Table).

TABLE

Sentinel Occupational Health Events—Occupationally Related Unnecessary Disease, Disability, and Untimely Death

Condition	Industry or occupation*	Agent
Pulmonary tuberculosis	Physicians, medical personnel, med lab workers	<i>Mycobacterium tuberculosis</i>
Silicotuberculosis	Quarrymen, sandblasters, silica processors, mining, metal foundries, ceramic industry	SiO ₂ + <i>Mycobacterium tuberculosis</i>
Plague	Shepherds, farmers, ranchers, hunters, field geologists	<i>Yersinia pestis</i>
Tularemia	Hunters, fur handlers, sheep industry workers, cooks, vets, ranchers, vet pathologists	<i>Francisella tularensis</i>
Anthrax	Shepherds, farmers, butchers, handlers of imported hides or fibers, veterinarians, veterinarian pathologists, weavers	<i>Bacillus anthracis</i>
Brucellosis	Farmers, shepherds, veterinarians, lab workers, slaughterhouse workers	<i>Brucella abortus, suis</i>
Tetanus	Farmers, ranchers	<i>Clostridium tetani</i>
Rubella	Medical personnel, intensive care personnel	Rubella virus
Hepatitis A	Day care center staff, orphanage staff, mental retardation institution staff, medical personnel	Hepatitis A virus
Hepatitis B	Nurses and aides, anesthesiologists, orphanage and mental institution staff, med lab personnel, general dentists, and oral surgeons, physicians	Hepatitis B virus
Non-A, non-B hepatitis	As for hepatitis A and B	Unknown
Rabies	Veterinarians, animal and game wardens, lab researchers, farmers, ranchers, trappers	Rabies virus
Ornithosis	Psittacine bird breeders, pet shop staff, poultry producers, veterinarians, zoo employees	<i>Chlamydia psittaci</i>
Hemangiosarcoma of the liver	Vinyl chloride polymerization industry	Vinyl chloride monomer
Malignant neoplasm of nasal cavities	Vintners Woodworkers, cabinet, furniture makers Boot and shoe industry Radium chemists and processors, dial painters Chromium producers, processors, users Nickel smelting and refining	Arsenical pesticides Hardwood dusts Unknown Radium Chromates Nickel
Malignant neoplasm of larynx	Asbestos industries and utilizers	Asbestos
Malignant neoplasm of trachea, bronchus, and lung	Asbestos industry and utilizers Topside coke oven workers Uranium and fluorspar miners Chromium producers and processors, users Nickel smelters, processors, users Smelters Mustard gas formulators Ion exchange resin makers, chemists	Asbestos Coke oven emissions Radon daughters Chromates Nickel Arsenic Mustard gas Bis(chloromethyl) ether, chloromethyl methyl ether Asbestos
Mesothelioma (MN of peritoneum) (MN of Pleura)	Asbestos industries and utilizers	Asbestos
Malignant neoplasm of bone	Dial painters, radium chemists and processors	Radium
Malignant neoplasm of scrotum	Automatic lathe operators, metalworkers Coke oven workers, petroleum refiners, tar distillers	Mineral/cutting oils Soots and tars, tar distillates
Malignant neoplasm of bladder	Rubber and dye workers	Benzdine, alpha and beta naphthylamine, auramine, magenta, 4-aminobiphenyl, 4-nitrophenyl Coke oven emissions
Malignant neoplasm of kidney, other, and unspecified urinary organs	Coke oven workers	Coke oven emissions
Lymphoid leukemia, acute	Rubber industry Radiologists	Unknown Ionizing radiation
Myeloid leukemia, acute	Occupations with exposure to benzene Radiologists	Benzene Ionizing radiation
Erythroleukemia	Occupations with exposure to benzene	Benzene
Hemolytic anemia, non-autoimmune	Whitewashing and leather industry Electrolytic processes, arsenical ore smelting Plastics industry Dye, celluloid, resin industry	Copper sulfate Arsine Trimellitic anhydride Naphthalene
Aplastic anemia	Explosives manufacture Occupations with exposure to benzene Radiologists, radium chemists and dial painters	TNT Benzene Ionizing radiation
Agranulocytosis or neutropenia	Occupations with exposure to benzene Explosives and pesticide industries Pesticides, pigments, pharmaceuticals	Benzene Phosphorus Inorganic arsenic
Methemoglobinemia	Explosives and dye industries	Aromatic amino and nitro compounds (e.g. aniline, TNT, nitroglycerin)
Toxic encephalitis	Battery, smelter, and foundry workers Electrolytic chlorine production, battery makers, fungicide formulators	Lead Inorganic and organic mercury
Parkinson's disease (secondary)	Manganese processing, battery makers, welders Internal combustion engine industries	Manganese Carbon monoxide

TABLE (Continued)

Condition	Industry or occupation*	Agent
Cerebellar ataxia	Chemical industry using toluene Electrolytic chlorine production, battery makers, fungicide formulators	Toluene. Organic mercury
Inflammatory and toxic neuropathy	Pesticides, pigments, pharmaceuticals Furniture refinishers, degreasing operations Plastic-coated-fabric workers Explosives industry Rayon manufacturing Plastics hydraulics, coke industries Battery, smelter, and foundry workers Dentists, chloralkali workers Chloralkali plants, fungicide makers, battery makers	Arsenic and arsenic compounds Hexane Methyl n-butyl ketone TNT CS ₂ Tri-o-cresyl phosphate Inorganic lead Inorganic mercury Organic mercury
Cataract	Plastics industry, paper manufacturing Microwave and radar technicians Explosives industries Radiologists Blacksmiths, glass blowers, bakers Moth repellent formulators, fumigators Explosives, dye, herbicide and pesticide industries Exposure	Acrylamide Microwaves TNT Ionizing radiation Infrared radiation Naphthalene Dinitrophenol, dinitro-o-cresol Excessive noise
Noise effects on inner ear	Lumberjacks, chain sawyers, grinders, chippers	Whole body or segmental vibration
Raynaud's phenomenon (secondary)	Vinyl chloride polymerization industry	Vinyl chloride monomer
Extrinsic allergic alveolitis	Farmers, baggassosis, bird fanciers, suberosis, malt workers, mushroom workers, maple bark disease, cheese washers, coffee workers, fish-meal workers, furriers, sequoia and other wood workers, millers	Various agents
Extrinsic asthma	Jewelry, alloy and catalyst makers Polyurethane, adhesive, paint workers Alloy, catalyst, refinery workers Solderers Plastic, dye, insecticide makers Foam workers, latex makers, biologists Printing industry Nickel platers Bakers Plastics industry Woodworkers, furniture makers Detergent formulators Coal miners Asbestos industries and utilizers Quarrymen, sandblasters, silica processors, mining, metal, and ceramic industries	Platinum Isocyanates Chromium and cobalt Aluminum soldering flux Phthalic anhydride Formaldehyde Gum arabic NiSO ₄ Flour Trimellitic anhydride Red cedar and other wood dusts Bacillus-derived exoenzymes Coal dust Asbestos Silica
Coalworkers' pneumoconiosis	Talc processors	Talc
Asbestosis	Beryllium alloy workers, ceramic and cathode ray tube makers, nuclear reactor workers	Beryllium
Silicosis	Cotton industry workers	Cotton, flax, hemp, and cotton-synthetic dusts
Talcosis	Refrigeration, fertilizer, oil refining industries Alkali and bleach industries Silo fillers, arc welders, nitric acid industry Paper and refrigeration industries, oil refining Cadmium smelters, processors Plastics industry	Ammonia Chlorine Nitrogen oxides Sulfur dioxide Cadmium Trimellitic anhydride
Chronic beryllium disease of lung	Solvent utilizers, dry cleaners, plastics industry	Carbon tetrachloride, chloroform, tetrachloroethane, trichloroethylene
Byssinosis	Explosives and dye industries Fire and waterproofing additive formulators Plastics formulators Fumigators, gasoline, fire extinguisher formulators	Phosphorus, TNT Chloronaphthalenes Methylenedianiline Ethylene dibromide
Acute bronchitis, pneumonitis, and pulmonary edema due to fumes and vapors	Disinfectant, fumigant, synthetic resin formulators	Cresol
Toxic hepatitis	Battery makers, plumbers, solderers Electrolytic processes, arsenical ore smelting Battery makers, jewelers, dentists Fluorocarbon formulators, fire extinguisher makers Antifreeze manufacture Formulators DBCP producers, formulators, and applicators	Inorganic lead Arsine Inorganic mercury Carbon tetrachloride
Acute or chronic renal failure	Leather tanning, poultry dressing plants, fish packing, adhesives and sealants industry, boat building and repair	Ethylene glycol Kepone Dibromochloropropane
Infertility, male		Irritants (e.g., cutting oils, solvents, phenol, acids, alkalis, detergents); allergens (e.g., nickel, chromates, formaldehyde, dyes, rubber products)
Contact and allergic dermatitis		

* Listings are examples only.

Adapted from Rutstein DD, Mullan RJ, Frazier TM, et al. Sentinel health events (occupational): a basis for physician recognition and public health surveillance. Am J Public Health 1983; 73(9):1054 (ref. 12)

If toxic exposures are identified or strongly suspected and an occupational or environmental cause seems likely, further follow-up inquiries may need to be made through the patient's labor union, the companies where he or she has been employed, company physicians, or state or local health departments. Information on toxic substances used in a workplace may be legally available to patients under the Records Access Standard and Hazard Communication Standard of the Occupational Safety and Health Administration and under state and local "right-to-know" laws.

Reporting and Referral. If the diagnostic interview indicates or raises the strong suspicion that disease is due to toxic occupational or environmental exposures, it is imperative that the physician report the case to state or local public health authorities. Many episodes of these diseases are in essence common-source outbreaks of highly preventable illness. Prompt reporting can lead to identifying additional cases earlier and to prevention by abating a common exposure source.

The physician may require access to specialized referral sources in occupational and environmental medicine. Two national organizations that maintain listings of occupational and environmental specialist physicians are the American College of Occupational and Environmental Medicine (Arlington Heights, Illinois) and the Association of Occupational and Environmental Clinics (Washington D.C.) Another valuable resource is the U.S. Public Health Service's National Institute for Occupational Safety and Health (Cincinnati, Ohio).

At Mount Sinai School of Medicine and The Mount Sinai Hospital, expert diagnostic and evaluation services in occupational and environmental medicine are available through the Mount Sinai-Irving J. Selikoff Clinical Center in Occupational and Environmental Medicine. This center is named in memory of the late Dr. Irving J. Selikoff, a pioneering physician in occupational medicine best known for his seminal work on the carcinogenesis of asbestos (8). The center is directed by staff of the Department of Community Medicine and is supported by a generous grant from the New York State Department of Health.

Establishing the Diagnosis of Occupational or Environmental Illness

If the history suggests an occupational or environmental etiology, two fundamental principles—biological plausibility and dose-response

relationship—help make a diagnosis of occupational or environmental disease.

Biological Plausibility. The likelihood that a disease is of occupational or environmental origin increases if the disease has previously been seen in other patients with the same or similar exposures, if a biologic mechanism is known, or if the disease has been seen in laboratory animals exposed experimentally to the chemical or to a similar chemical. Bear in mind, however, that many thousands of chemicals to which workers are exposed regularly in industry and that have been dispersed into the environment have never been laboratory tested for their toxicity. Therefore, the possibility always exists of diagnosing a disease entity never previously recognized—for example, malignant mesothelioma in workers exposed to asbestos, hepatic angiosarcoma in workers exposed to vinyl chloride, and cancer of the bladder in aniline dye workers.

Dose-Response Relationship. The likelihood of occupational or environmental causation increases if the disease occurs more commonly and more seriously in the more heavily exposed members of a population. Bear in mind, however, that in the case of occupational and environmental carcinogens, there are no threshold levels of exposure below which safety is assured; any exposure to these agents is potentially carcinogenic, although heavier exposures carry greater risks. Also, agents that are allergens or chemical sensitizers can cause symptoms at very low exposure levels.

Sentinel Health Events. To assist physicians to establish linkages between occupational exposures and disease, Rutstein and colleagues developed the concept of the sentinel health event (11), defined as "an unnecessary disease, disability, or untimely death whose occurrence signals a failure of prevention." Examples include unnecessary maternal deaths, an outbreak of cholera, or a single case of poliomyelitis.

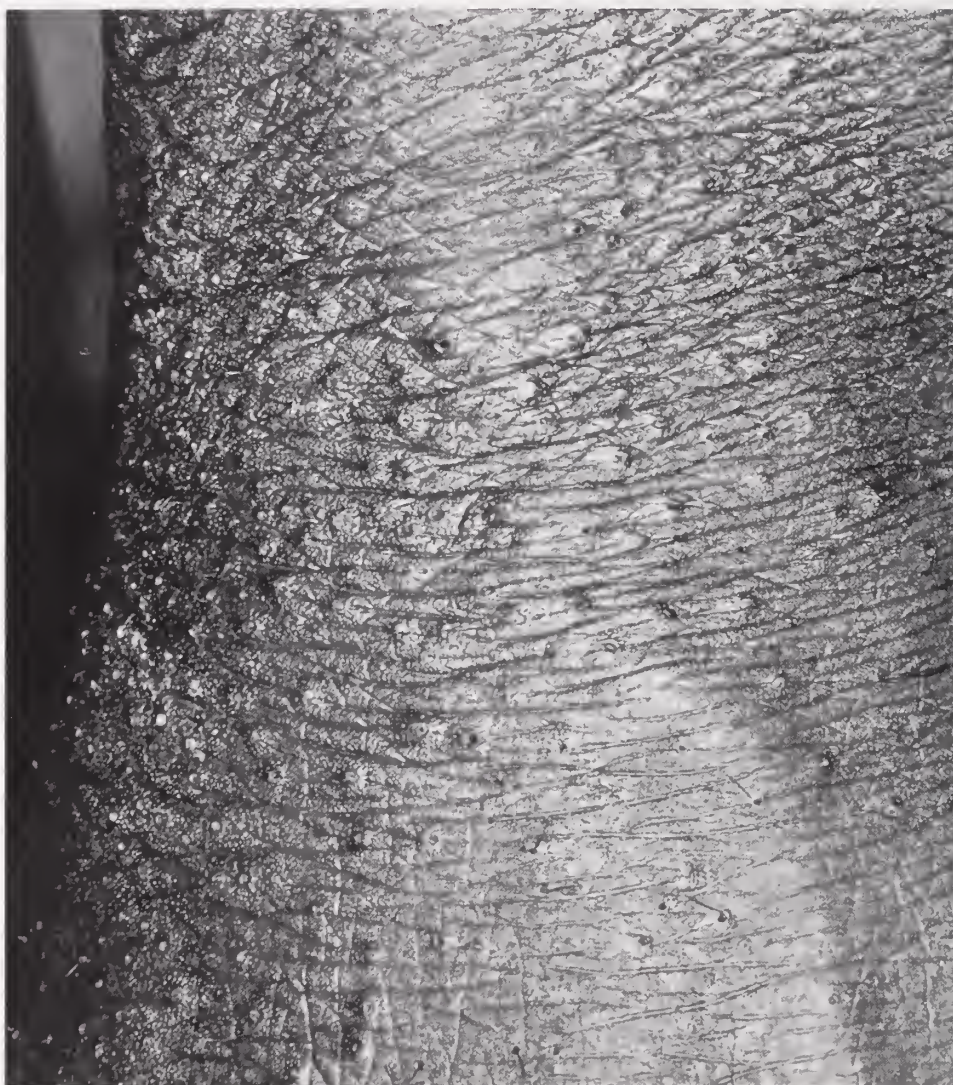
Extending the concept of "sentinel health events" to occupational and environmental exposure, Rutstein and colleagues defined a "sentinel health event (occupational)" as "an unnecessary disease, disability or untimely death which is occupationally related" (12). By scanning a selected list of these events (Table), physicians can identify work-related illnesses or exposures that may occur in their patients. They can also identify from this list occupations and industries potentially pertinent in the locality of their medical practice. This list is an accessible starting point for developing competence in the differential di-

agnosis of occupational and environmental disease (13).

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Tar Melanosis



Tar melanosis occurs in workers exposed to tar or other hydrocarbons. It is characterized by a pruritic photosensitivity reaction consisting of erythema, edema, and blistering at sun-exposed body sites. When the acute reaction has subsided, the patients are left with hyperpigmentation and follicular hyperkeratosis, shown here in a black tar worker.—*Mark Lebwohl, M.D., and Jim Baral, M.D., Department of Dermatology, The Mount Sinai Hospital*

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Breast Cancer and Family History:

A Multivariate Analysis of Levels of Tumor HER2 Protein and Family History of Cancer in Women Who Have Breast Cancer

STEVEN LEHRER, M.D., PATRICIA LEE, PAUL TARTTER, M.D., BRENDA SHANK, M.D., PH.D., AND
STEVEN T. BROWER, M.D.

Abstract

Background: The HER2 gene, located on the long arm of chromosome 17, codes for a protein with the characteristics of a growth factor receptor. In a preliminary study, we reported that high levels of tumor HER2 (erbB-2/neu) protein are associated with a family history of breast cancer (that is, one or more female blood relatives with breast cancer).

Methods: We have now collected a larger number of subjects (94) and performed a multivariate analysis of the independent variables family history of breast cancer, tumor estrogen receptor, age, and tumor DNA index. Family history of breast cancer was assessed by questioning the patient, in many cases by telephone.

Results: HER2 levels were significantly higher in women with a family history of breast cancer ($p = 0.015$, two-tailed t -test). The 27 women with family history were predominantly postmenopausal, mean age 61 ± 2.3 (mean $\pm$ SEM), versus a mean age of 56 ± 1.7 for the 67 women with no family history. Of the 27 women with a family history of breast cancer, 13 had a first-degree relative (mother or sister) with the disease. The remaining 14 women had other relatives (grandmothers, aunts, cousins, or a niece) with breast cancer. The results of multiple linear regression analysis, with HER2 as the dependent variable, showed that family history of breast cancer was significantly associated with elevated HER2 levels in the tumors ($p = 0.0038$), after controlling for the effects of age, tumor estrogen receptor, and DNA index.

Conclusions: The association of family history of breast cancer and elevated tumor HER2 protein suggests that postmenopausal familial breast cancer may be associated with altered HER2 expression.

THE HER2 GENE, located on the long arm of chromosome 17, codes for a protein with the characteristics of a growth factor receptor (1, 2). Its ligand, a molecule which binds to the receptor and activates it, may belong to a family of proteins called heregulins (3). HER2 protein overexpression in breast cancers may be associated with poor prognosis (4), although this connection is controversial (5, 6).

HER2 overexpression is also associated with higher tumor mitotic activity (7,8) and young age (6). HER2 overexpression is negatively correlated with tumor estrogen receptor and progesterone receptor content (9). HER2 overexpression is found in over 90% of ductal carcinomas in situ of the comedo type, whereas other subtypes, such as the cribriform, solid, or papillary, rarely overexpress HER2 (6).

In a preliminary study (10), we reported that high tumor HER2 protein levels are also associated with a family history of breast cancer. We have now collected a larger number of subjects and performed a multivariate analysis to control for the effects of other factors which affect HER2 expression.

From the Departments of Radiation Oncology (SL, PL, BS) and Surgery (PT, STB), The Mount Sinai Medical Center, New York, NY. Address correspondence and reprint requests to Dr. Steven Lehrer, Box 1236, Radiation Oncology, The Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029.

Methods

We measured HER2 protein levels in 94 women who had breast cancer excised in Mount Sinai Medical Center in 1991, 1992, and 1993. We included in the study only cases in which there was sufficient tumor tissue to determine HER2 protein level, estrogen receptor protein level, and DNA index.

Of the breast cancer cases, 57 (60.6%) were stage T1, 33 (35.1%) were stage T2, and 4 (4.3%) were stage T3. The smallest tumor was 0.6 cm; the largest was 10 cm. In 50 cases (53.2%) there was no node involvement; in 44 cases (46.8%) there was node involvement. A total of 73 cases (77%) were classified as ductal carcinoma, 11 cases (11.7%) as lobular carcinoma, 5 cases (5.3%) as mixed ductal and lobular carcinoma, and 4 cases as of other histologic structure (malignant phyllodes tumor, comedocarcinoma, colloid carcinoma). Ten cases were classified as in situ, and 84 cases as infiltrating.

HER2 protein was extracted from frozen breast tumor tissue and assessed by a well-behaved competitive enzyme immunoassay (EIA). Homogenized tumor tissue is trypsinized, centrifuged, and incubated with tris lysis buffer (10 mM tris-HCl, pH 7.6, 1.5 mM EDTA, 10% glycerol, 0.1% sodium azide). The proteins are then detergent extracted (11). After centrifugation, supernatants are collected and protein values determined by BCA assay (Pierce Chemical Company).

The enzyme immunoassay employs an affinity-purified sheep polyclonal antibody which was generated against a synthetic peptide composed of 19 amino acids derived from the cytoplasmic domain of the human c-erbB-2 (HER2) oncoprotein. This peptide has two amino acid substitutions which differ from the corresponding aligned sequence in rat neu. The synthetic peptide has approximately 50% alignment with the epidermal growth factor-receptor (EGFR) sequence. The immunogenic synthetic HER2 peptide is used as the calibrator for the assay. The antibody detects bands at 170 kDa and 185 kDa on immunoblots of SkBr-3 cell membrane preparations which produce high levels of HER2 protein. HER2 is the membrane-associated 185 kDa oncoprotein detected by this antibody; the 170 kDa band represents a degradation product of the 185 kDa HER2 oncoprotein. These bands can be blocked by preincubation of the antibody with the immunogenic synthetic peptide. The antibody does not recognize any bands on immunoblots prepared from A431 cells which produce high levels of EGFR. Furthermore, specificity of the antibody has been tested by Western blot; there is

no cross-reactivity with EGFR produced by breast cancer cell lines, or any other significant cross-reactivity (data on file, Dianon Systems, Stratford, CT). The antibody is specially produced for Dianon Systems and is not commercially available.

Two quality control specimens are run in each assay to ensure day-to-day precision. The negative control consists of a pool of 1,000 human breast biopsy specimens, which possesses a HER2 concentration of less than 2,000 fmol/mL. The positive control consists of SKBR-3 breast cancer cells (12), which produce HER2 at a level of greater than 2,000 fmol/mL, the cutoff point for overexpression.

The cutoff point was established in two ways: (a) 14 specimens of pathologically proven benign tissue, removed during reduction mammoplasty and fresh frozen, were assayed for HER2. Only one of these specimens had HER2 concentration greater than 2,000 fmol/mg; (b) more than 800 breast cancer biopsies were assayed for HER2. Thirty percent of the specimens were found to have HER2 levels of greater than 2,000 fmol/mg.

The results of the HER2 EIA are normalized by the amount of total protein extracted from the tissue specimen. The total protein in the extracted tissue is measured by a commercial dye assay method (Biorad Laboratories). Results of the HER2 assay correlate well, relative to percent positive cases, with those obtained by immunohistochemistry (data on file, Dianon Systems, Stratford, CT).

Specimens for flow cytometric analysis were prepared using a modification of the Thornthwaite procedure (13). The samples were analyzed with the Coulter Epics-XL Flow Cytometer (Coulter Corporation, Hialeah, FL). Analysis of ploidy was performed using Verity Software (Verity Software House, Topsham, ME) with a minimum sample size of 10,000 cells. DNA indices of 1.00 were considered diploid; those above 1.00 were considered aneuploid. Calibration for true diploidy was done using normal lymphocytes.

Tumor estrogen receptor was determined by enzyme immunoassay (EIA) (Abbott, North Chicago, IL). The cutpoint of the assay, 15 fmol/mg, was determined by the manufacturer. All assays were performed by Dianon Systems, Stratford, CT.

Family history of breast cancer was assessed by questioning the patient, in many cases by telephone. In other cases, the patient was interviewed in person. Family history was defined as any female blood relative with breast cancer. No attempt was made to verify family history by contacting other family members or their physicians.

To do multivariate analysis, we logarithmically transformed HER2 and estrogen receptor values to normalize variances. Statistical analyses were done with the SPSS System (14).

Results

HER2 levels were significantly higher in women who reported a family history of breast cancer ($p = 0.015$, two-tailed t -test, Fig.). In 67 women without a family history, log of the mean tumor HER2 level was 2.99 ± 0.034 (mean $\pm$ SE), minimum value was 2.39, maximum value was 3.66. In 27 women with a family history, log of the mean tumor HER2 level was 3.15 ± 0.057 , minimum value was 2.57, maximum value was 3.91. The log of the mean difference was 0.1587 (0.031–0.286, 95% CI).

The 27 women reporting a family history were predominantly postmenopausal, mean age 61 ± 2.3 (mean $\pm$ SEM), versus a mean age of 56 ± 1.7 for the 67 women reporting no family history; there is no significant age difference in these two groups ($p = 0.19$, two-tailed t -test).

Of the 27 women with a family history of breast cancer, 13 (13.8% of all cases) had a first-degree relative (mother or sister) with the disease. This is comparable to the 12% of cases with an affected first-degree relative reported by Slattery and Kerber (15). The remaining 14 women had other relatives (grandmothers, aunts, cousins, or a niece) with breast cancer. There was no significant difference in HER2 levels between women who had a first-degree relative with breast cancer and women who had relatives of other degrees with breast cancer. There were too few patients to compare HER2 levels in women with affected first-degree relatives to women without family history.

The results of multiple linear regression analysis (Table), in which log HER2 was the dependent variable, were significant overall ($F = 3.4$, $p = 0.01$). DNA index, age, and tumor estrogen receptor concentrations showed the same effects on HER2 levels that have been previously demonstrated. However, of these, only the effect of DNA index ($p = 0.02$) was significant. Moreover, family history of breast cancer was significantly associated with elevated HER2 levels in the tumors ($p = 0.0038$).

There was no significant difference in HER2 levels between in situ and infiltrating tumors, nor was there a significant association between tumor size, node involvement, or stage and tumor HER2.

Discussion

Recently, a familial breast-ovarian cancer gene, BRCA1, has been localized to the long arm

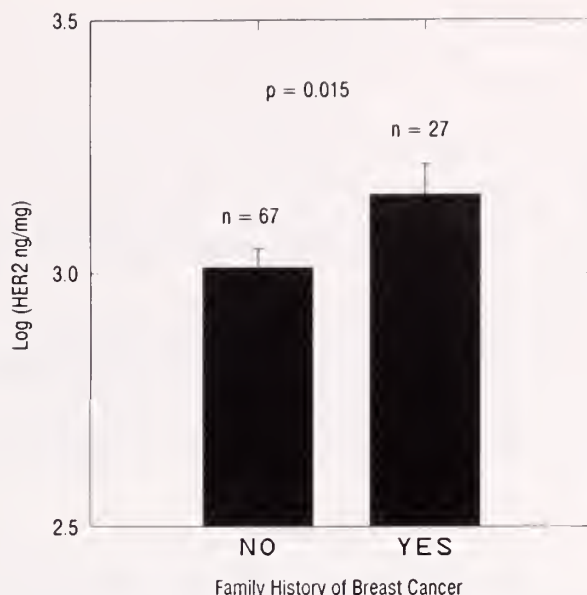


Fig. Log HER2 protein (mean $\pm$ SD) in tumors of women with and without a family history of breast cancer. Number of cases in each group is indicated above the corresponding error bar.

of chromosome 17 (16, 17). This gene, associated with breast cancer in women under age 45, is not the HER2 gene (2, 18), which is also located on the long arm of chromosome 17. In addition, there is evidence implicating at least two genes on the short arm of chromosome 17 in breast cancer carcinogenesis (19, 20). Finally, although some studies suggest that the HER2 gene is not involved in the genesis of breast cancer (21), at least three new HER2 mutations in breast tumors have recently been identified (22–24).

Moreover, there is evidence that HER2 is involved in breast cancer initiation. For example, HER2 alterations are present in all clinical stages of the disease, are maintained during metastatic spread, are homogeneously present throughout tumor sections, and are present in in situ as well as infiltrating tumors (25). Our own data, as mentioned, also showed no significant difference in HER2 levels between in situ and infiltrating tumors. Therefore, HER2 alter-

TABLE
Multiple Linear Regression Showing Effects of Family History of Breast Cancer, DNA Index, Log Estrogen Receptor (ER), and Age on Log HER2 in the Tumors of 94 Women

Variable	Regression coefficient	Standard error	T	P
Family history	0.19	0.06	3.0	0.0038
DNA index	0.14	0.06	2.3	0.02
Log ER	−0.005	0.03	−0.16	0.87
Age	−0.002	0.002	−1.0	0.3

ations appear early and may be a causal factor (26).

HER2 is also implicated in animal studies of mammary tumor development, for example in mammary cancer in transgenic mice (27). And early mutations of HER2 are implicated in the development of other tumors, for example nitrosourea-induced neural malignancies in rat Schwann cells (28).

Based on these studies and on our finding of elevated HER2 protein in breast tumors associated with family history of breast cancer, we hypothesize that postmenopausal familial breast cancer may be associated with altered HER2 expression.

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Breast Cancer and Family History:

Levels of Lipid-Associated Sialic Acid in Plasma and Absent Family History of Breast Cancer in Women Who Have Breast Tumors

STEVEN T. BROWER, M.D., PAUL TARTTER, M.D., STEPHANIE WEISS, ALBERT A. LUDERER, PH.D., AND STEVEN LEHRER, M.D.

Abstract

Background: Breast cancer has a strong genetic component, and at least two breast cancer genes exist. But these genes probably play little role in most breast cancers. Other factors, such as environmental estrogens and diet, may cause the genetic changes involved in the genesis of sporadic breast cancer. A method of observing genetic changes indirectly might be to measure tumor markers known to be associated with breast cancer.

Methods: We measured, by biochemical extraction and partition, lipid-associated sialic acid in plasma (LASA-P), a circulating tumor marker, in a group of 239 women with benign or malignant breast tumors.

Results: The concentration of LASA-P was elevated in women with both benign and malignant tumors and no family history of breast cancer ($p = 0.046$, one-way ANOVA). Because LASA-P levels rise with age and number of pregnancies, we analyzed our data using multiple linear regression. Benign versus malignant character of the tumor, family history of breast cancer, number of pregnancies, and age were the independent variables. Family history of breast cancer had a significant effect on LASA-P levels ($p = 0.0146$) independent of the effects of age ($p = 0.011$), number of pregnancies (0.012), and whether the tumor was benign or malignant ($p = 0.31$).

Conclusions: We hypothesize that elevated LASA-P in women with breast tumors and no family history of breast cancer is a result of the genetic changes occurring in nonfamilial breast cancer. These genetic changes, possibly related to environmental estrogens or other environmental factors, are distinct from the changes due to mutations of BRCA1 or other familial breast cancer genes. Moreover, the elevation of LASA-P suggests that the surface membranes of breast cancer may differ in composition. Further study may lead to exact characterization of the genetic and cell membrane changes associated with familial and nonfamilial breast tumors, and perhaps to better methods of breast cancer prevention and treatment.

BREAST CANCER has a strong genetic component; there are at least two breast cancer genes, BRCA1 and BRCA2 (1, 2). But these two genes

probably play little role in most breast cancers (2). Indeed, 90%–95% of “sporadic” breast cancers are unlikely to be due to inherited susceptibility (2). Thus, other factors, such as environmental estrogens and diet, may cause the genetic changes involved in the genesis of sporadic breast cancer (3, 4).

A method of observing genetic changes indirectly might be to measure tumor markers known to be associated with breast cancer. For example, levels of one circulating tumor marker, lipid-associated sialic acid in plasma (LASA-P), are ab-

From the Departments of Surgery (STB, PT, SW) and Radiation Oncology (SL), the Mount Sinai School of Medicine, New York; and Dianon Systems, Inc. (AAL), Stratford, Connecticut. (AAL is scientific director of Dianon Systems, a clinical laboratory, which performs LASA-P assays for physicians.) Address correspondence and reprint requests to Dr. Steven Lehrer, Box 1236, The Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029.

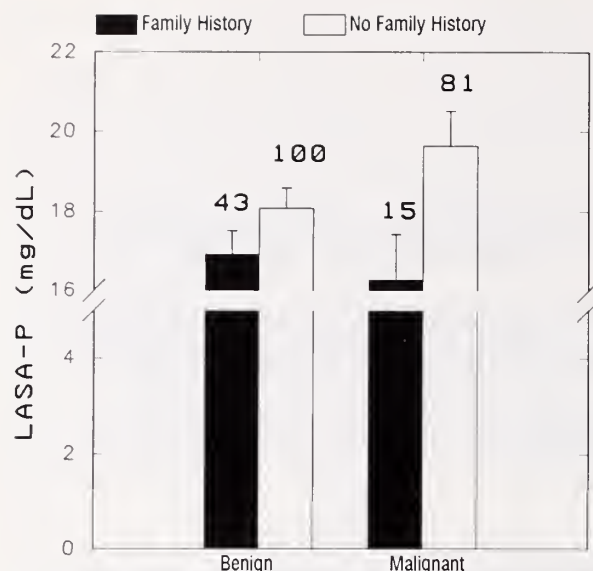


Fig. Family history of breast cancer and LASA-P levels (mean $\pm$ SEM) in 239 women with benign and malignant breast tumors. Number of women in each group indicated above corresponding error bar.

normally high in the plasma and serum of patients with gynecologic malignancies, including breast cancer (5–7).

We have measured LASA-P in a series of women with breast tumors. We now report that LASA-P is elevated in women with benign and malignant breast tumors who have no family history of breast cancer.

Methods

We studied 239 women with benign or malignant breast tumors surgically treated in The Mount Sinai Medical Center between 1991 and 1994. Cases were selected for study if the family history was known and LASA-P had been measured. Family history was assessed by questioning the patient. No attempt was made to contact affected relatives.

Plasma specimens to be assayed for LASA-P were collected in tubes containing ethylenediaminetetraacetic acid (EDTA) and frozen until tested. LASA-P was determined by the procedure of Katopodis and Stock (8). Total lipid was extracted from 45 μ L of plasma with 3 mL of chloroform/methanol (2/1 by volume) at 4–5°C. The extract was partitioned with 0.5 mL of cold distilled water, and the aqueous phase containing the sialolipid fraction was precipitated with 50 μ L of a 1 g/mL suspension of phosphotungstic acid. After centrifugation (5 min, room temperature, 750 $\times$ g), the supernatant fluid was aspirated, the precipitate was determined by the re-

sorcinol method (9, 10). The extracted blue color was assessed spectrophotometrically at 580 nm, and the sialic acid was calculated by use of a standard curve constructed from data on *N*-acetylneuraminic acid (purity 98%, Sigma Chemical Co., St. Louis, MO) in amounts ranging from 5 to 20 μ g per tube (6). Dianon Systems, Stratford, CT, performed all assays. Statistical analysis was done with the SPSS System (11).

Results

The average age of the 239 women studied was 48.4 years. The youngest woman was 16, the oldest 84. Women with malignant tumors were, on average, ten years older than women with benign tumors. Of the 15 breast cancer patients with a family history of breast cancer, six had a mother with breast cancer, and one had a sister with breast cancer. The others had more distant relatives with breast cancer (grandmothers, aunts, a cousin, or a niece). Of the 43 women with benign breast tumors and a family history of breast cancer, 16 had mothers with breast cancer, two had sisters, and the others had more distant relatives with breast cancer (grandmothers, aunts, cousins, or a niece).

Of the women with malignant tumors and a family history of breast cancer, 60% had ductal carcinoma, 33% had lobular carcinoma, and 7% had mixed ductal and lobular carcinoma. Of the women with malignant tumors and no family history of breast cancer, 83% had ductal carcinoma, 8% had lobular carcinoma, and 9% had mixed ductal and lobular carcinoma.

The concentration of LASA-P was elevated in women with both benign and malignant breast tumors and no family history of breast cancer ($p = 0.046$, one-way ANOVA, Fig.). Because LASA-P levels rise with age and number of preg-

TABLE
Multiple Linear Regression Analysis of Effect of Family History of Breast Cancer on Levels of LASA-P in 239 Women with Breast Tumors

Variable	b	SE	t Test	p
Family history*	2.27	0.92	2.46	0.0146
Histologic character†	0.90	0.89	1.01	0.31
Pregnancies‡	1.24	0.49	2.54	0.01
Age	0.079	0.031	2.56	0.011

b, regression coefficient.

* Absent or present.

† Benign vs malignant.

‡ Zero, one, two or more.

nancies (12), we analyzed our data using multiple linear regression. Benign versus malignant character of the tumor, family history of breast cancer, number of pregnancies, and age were the independent variables (Table). Family history of breast cancer had a significant effect on LASA-P levels ($p = 0.0146$) that was independent of the effects of age ($p = 0.011$), number of pregnancies ($p = 0.012$), and whether the tumor was benign or malignant ($p = 0.31$). There was no significant correlation of LASA-P levels with estrogen receptor (ER) ($r = 0.13$) or progesterone receptor (PR) ($r = 0.06$) in the malignant tumors. Because ER and PR were measured only in malignant tumors, ER and PR were not included in the multiple regression analysis.

Discussion

LASA-P is a biomarker useful in a wide range of malignancies. It reflects alteration in the surface membrane of tumor cells. The LASA-P assay measures total gangliosides and glycoproteins (6). Elevated LASA-P levels in breast cyst fluid have been associated with increased risk of breast cancer (13). Also, LASA-P levels are higher in women with benign or malignant breast tumors than in controls. Patel et al. (14) found LASA-P levels (mean $\pm$ SEM, in mg/g) of 17.07 ± 0.607 for controls, 23.7 ± 1.66 for benign tumors, and 28.03 ± 1.9 for malignant tumors.

Some conditions other than cancer affect LASA-P. Among them are myocardial infarction (15), infections, rheumatoid arthritis, and collagen degeneration.

We hypothesize that the elevated LASA-P in women with breast tumors and no family history of breast cancer is a result of the genetic changes occurring in nonfamilial breast cancer. These genetic changes, possibly related to environmental estrogens or other environmental factors, are distinct from the changes due to mutations of BRCA1 or other familial breast cancer genes. Moreover, the elevation of LASA-P suggests that the surface membranes of breast tumor cells from women without and women with a family history of breast cancer may differ in composition. Further study may lead to exact characterization of the genetic and cell membrane changes associ-

ated with familial and nonfamilial breast tumors, and perhaps to better methods of breast cancer prevention and treatment.

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Mortality in Hospitalized Patients with Hypoglycemia and Severe Hyperglycemia

ALEX STAGNARO-GREEN, M.D., FACP, MARY KAY BARTON, M.D., PATRICIA L. LINEKIN, RN, BSN, CDE, EILEEN CORKERY, RN, MSN, CDE, KATHARINE DEBEER, B.A., AND SHEILA H. ROMAN, M.D., MPH

Abstract

Background: We designed a study to determine the incidence, cause, and implications of hypoglycemia (≤ 2.7 mmol/L, 49 mg/dL) and severe hyperglycemia (≥ 22.2 mmol/L, 400 mg/dL) in in-patients at an urban tertiary medical center.

Methods: A daily computer search of the Laboratory Information System identified all hospitalized patients with hypoglycemia and severe hyperglycemia during a 49-day period. Chart review was used to assess demographic information, risk factors, and epidemiologic variables. The eventual outcome of the hospitalization was obtained by follow-up.

Results: The incidence of hypoglycemia was 1.5%, and of hyperglycemia, 1.9%. Seventy-six percent of the hypoglycemic patients and 16% of the hyperglycemic patients had no prior history of diabetes. The mortality rate for hypoglycemic patients was 22.2%; for hyperglycemic patients it was 11.1%. For all other hospitalized patients it was 2.3% ($p < 0.0001$). Mortality rates for the black and Hispanic patients who were hypoglycemic (30% and 46%) were significantly higher than for white patients (6%, $p < 0.01$).

Conclusions: Hypoglycemia and severe hyperglycemia are not uncommon in hospitalized patients and serve as metabolic markers for patients at increased risk for in-hospital mortality. Early identification of at-risk patients and the impact of aggressive treatment of their underlying disease processes should be evaluated in future studies.

DATA on the incidence and implications of hypoglycemia and hyperglycemia during hospitalization are limited. Fischer, Less, and Newman (1) performed a retrospective chart review of adult patients admitted to a tertiary-care medical center who exhibited hypoglycemia during a six-month period. They reported that only 45% of the 94 patients who exhibited hypoglycemia had diabetes, and the hospital mortality rate for all hy-

poglycemic patients was a surprisingly high 27%. A prospective study of the hospital prognosis of patients who had had a myocardial infarction (MI), reported by O'Sullivan et al. in 1991, found a higher mortality rate in patients without a prior history of diabetes who exhibited hyperglycemia than in patients who had had an MI but whose blood glucose levels were normal (22% vs 7%, $p 0.001$) (2).

Through our prospective quality assurance monitoring program at The Mount Sinai Medical Center, we observed that hypoglycemia and marked hyperglycemia were common in hospitalized patients who did and those who did not have a history of diabetes. Consequently, we performed a prospective study assessing the incidence, causes, and hospital outcomes of individuals with hypoglycemia and severe hyperglycemia. Hypoglycemia and hyperglycemia were frequent in-hospital events at this tertiary-care medical cen-

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From the Division of Endocrinology and Metabolism, Department of Medicine, and the Department of Nursing (PLL, EC), Mount Sinai School of Medicine, New York, NY. Address correspondence and reprint requests to Alex Stagnaro-Green, MD, Box 1255, The Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029.

TABLE 1

Clinical Characteristics of 153 Hospitalized Hypoglycemic and Hyperglycemic Patients by Survival of Hospitalization (mean $\pm$ SEM)

Clinical characteristics	Hypoglycemic pts			Hyperglycemic pts		
	Lived	Died	p*	Lived	Died	p*
Age, years	39.9 $\pm$ 3.8	53.9 $\pm$ 5.0	ns	55.9 $\pm$ 2.2	68.6 $\pm$ 4.6	0.049
Blood sugar, mmol/L (mg/dL)	2.2 $\pm$ 0.1 (40 $\pm$ 2)	1.9 $\pm$ 0.1 (34 $\pm$ 0.1)	ns	30.0 $\pm$ 1.6 (545 $\pm$ 29)	24.8 $\pm$ 0.6 (487 $\pm$ 11)	ns
Creatinine, mmol/L (mg/dL)	177 $\pm$ 35 (2.0 $\pm$ 0.4)	274 $\pm$ 62.0 (3.1 $\pm$ 0.7)	ns	248 $\pm$ 27 (2.8 $\pm$ 0.3)	159 $\pm$ 35 (1.8 $\pm$ 0.4)	ns
WBC count, 10 ⁹ /L (cu mm)	12.0 $\pm$ 0.9 (12000 $\pm$ 900)	18.2 $\pm$ 4.4 (18200 $\pm$ 4400)	0.03	12.2 $\pm$ 0.6 (12200 $\pm$ 600)	13.9 $\pm$ 2.5 (13900 $\pm$ 2500)	ns
Hematocrit, %	36.2 $\pm$ 1.2	27.3 $\pm$ 1.9	0.0006	33.0 $\pm$ 0.9	33.3 $\pm$ 2.2	ns
SGPT, U/L	130.9 $\pm$ 47	148 $\pm$ 88	ns	29.0 $\pm$ 3	38.0 $\pm$ 14	ns

* Lived vs. died.

ter, and both were associated with a marked increase in mortality.

Research Design and Methods

A daily computer search through the Laboratory Information System (LIS) at The Mount Sinai Medical Center identified all patients with serum glucose levels equal to or less than 2.7 mmol/L (49 mg/dL) or greater than or equal to 22.2 mmol/L (400 mg/dL). Glucose determinations were performed in the chemistry laboratory utilizing the glucose oxidase method. The population studied included all in-patients at The Mount Sinai Medical Center for a 49-day period. Chart review was used to assess for a number of variables, including age, sex, race, diagnoses, history of diabetes, nutritional status, risk factors for hypoglycemia and hyperglycemia, and a variety of laboratory parameters. In each patient a cause for the hypoglycemia or hyperglycemia was determined. Renal disease was defined as a creatinine level equal to or above 177 mmol/L (2 mg/dL), and liver disease was defined as an SGPT greater than or equal to 159 U/L (three times the upper limit of normal).

The eventual outcome of the hospitalization was ascertained by follow-up. Data was entered and analyzed on the CLINFO Data Management System. Statistical analyses included *t*-tests, ANOVAs, chi-squares, and trend analysis where appropriate. Significance was set at *p* < 0.05.

Results

Incidence. There were 106 episodes of hypoglycemia in 80 patients and 166 episodes of hyperglycemia in 104 patients during the time interval studied. There was a total of 5491 admissions during the study period, yielding an

incidence of hypoglycemia of 1.5% (80/5491) and an incidence of hyperglycemia of 1.9% (104/5491). Thirteen patients had both a hypoglycemic and a hyperglycemic episode. Patients who exhibited both hypoglycemia and hyperglycemia were classed for analysis by the metabolic condition they first exhibited.

Hypoglycemia. Eight of the 80 (10%) patients classified as hypoglycemic had spurious results. Determination that the laboratory test was erroneous was based on a lack of symptoms of hypoglycemia, repeat glucose determination that was normal without intervention, and an absence of further episodes of decreased glucose levels. The hypoglycemia in these 8 individuals was determined to be false either because blood samples were not assayed for a prolonged period of time or because white blood cell counts were high. All subsequent analyses of the hypoglycemic patients excluded these 8 patients. Twenty-two per cent (16/72) of the hypoglycemic patients died during their hospitalization. None of the deaths were secondary to hypoglycemia.

The majority of patients (76%) who were hy-

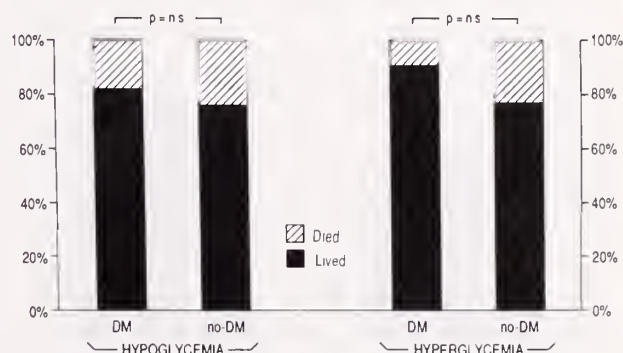


Fig. 1. History of diabetes prior to admission in patients with hypoglycemia and hyperglycemia grouped by eventual outcome of hospitalization (lived vs died). DM, diabetes mellitus; No-DM, no history of diabetes mellitus.

TABLE 2

Risk Factors Present in 153 Hospitalized Hypoglycemic and Hyperglycemic Patients by Survival of Hospitalization (%)

Risk factor	Hypoglycemic pts			Hyperglycemic pts		
	Lived	Died	p	Lived	Died	p
Infection	36%	69%	0.02	59%	78%	ns
Sepsis	14%	50%	0.005	18%	22%	ns
Cancer	11%	38%	0.02	10%	44%	0.02
Liver disease (≥ 159 U/L)	15%	21%	ns	0	0	ns
Steroids	5%	0	ns	11%	33%	ns
Renal disease (≥ 2.0 mg/dL)	18%	47%	0.02	42%	33%	ns
Neonate	16%	6%	ns	0	0	ns
Inadequate oral intake	68%	88%	ns	46%	78%	ns
Renal transp	0	0	ns	8%	0	ns
Liver transp	2%	0	ns	1%	0	ns
Neuropathy	11%	0	ns	13%	0	ns
Retinopathy	4%	0	ns	13%	0	ns
Shock	2%	0	ns	0	0	ns

poglycemic had no history of diabetes. The mortality rate of the 17 hypoglycemic patients with diabetes and without a history of diabetes was similar (Fig. 1). The relationship between mortality and race, however, proved highly significant statistically (Fig. 2). Although mortality rates among the black and Hispanic patients were similar (30% vs. 46%), both groups had a statistically significant higher mortality rate than did the white patients (6%) (p 0.014 and p 0.001, respectively).

The mean blood sugar levels for the hypoglycemic groups were not different (Table 1). The group of hypoglycemic patients who died was older than the group who survived, but age difference did not reach statistical significance (p 0.07). The hypoglycemic patients who died had significantly higher white blood cell counts and significantly lower hematocrits than the hypogly-

cemic patients who survived (Table 1). Risk factors significantly higher in the hypoglycemic patients who died included infection, sepsis, cancer, and renal insufficiency (Table 2). The most common causes for hypoglycemic episodes in the patients who died were renal disease, inadequate oral intake, liver disease, and sepsis (25%, 25%, 19%, and 19% respectively). For hypoglycemic patients who survived, the most common causes were inadequate oral intake, neonate status, and sepsis (34%, 16%, and 11%).

Demographic variables, risk factors, and etiologies for the hypoglycemic patients were also analyzed by whether or not the patient had diabetes. Mean age (63.0 ± 2.9 years vs 36.8 ± 3.8 years, p 0.0004) and serum creatinine (336 ± 80 mmol/L vs 150 ± 27 mmol/L, p 0.0052) (3.8 ± 0.90 mg/dL vs 1.70 ± 0.31 mg/dL, p 0.0052) were higher in the diabetic patients. Analysis of risk factors confirmed the higher incidence of renal disease (41% vs 18%, p 0.051) in the hypoglycemic patients who had diabetes.

There was no association between the degree of hypoglycemia or the number of hypoglycemic episodes and mortality. However, trend analysis revealed a higher mortality rate in individuals with a greater number of risk factors for hypoglycemia (p 0.043).

Analysis of the mean age and laboratory parameters of the three ethnic groups was performed to determine the cause of the higher mortality rate in the black and Hispanic patients. The mean ages of the three groups were not statistically different (white, 46 years; black, 45 years; Hispanic, 35 years; p 0.44). The only laboratory parameter that was significantly different was serum creatinine. The mean creatinine level was higher in the black population (345 mmol/L, 3.90 mg/dL) than in the Hispanic (168 mmol/L, 1.90 mg/dl) and white (125 mmol/L, 1.41 mg/dL) populations (p 0.005).

Hyperglycemia. Spurious glucose elevations—so classified when the patient's chart contained no other hyperglycemic values—were found in 23/104 (22%) patients classified as hyperglycemic. These spurious hyperglycemic laboratory values were felt to be secondary to blood being drawn above intravenous lines or inappropriate blood extractions from central lines. All analyses of the hyperglycemic patients excluded these 23 individuals. Eleven per cent (9/81) of the hyperglycemic patients died during their hospitalization.

The majority of patients who exhibited hyperglycemia were known diabetics (84%). There was a similar mortality rate among hyperglyce-

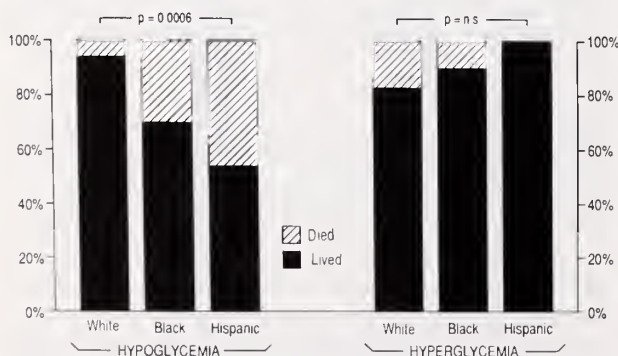


Fig. 2. Racial distribution of patients with hypoglycemia or hyperglycemia grouped by eventual outcome of hospitalization (lived vs. died).

mic patients with and without a history of diabetes (9% vs 23%, $p = \text{n.s.}$, Fig. 1). In the two groups with hyperglycemia there were no statistically significant racial differences in eventual patient outcome (Fig. 2).

The mean age of the hyperglycemic patients who died was significantly higher than that of those who survived hospitalization (Table 1). There were no significant laboratory differences between the two hyperglycemic groups (Table 1). Cancer was more common in the patients with hyperglycemia who died, but no other risk factor distinguished the groups from each other (Table 2). The most common cause of hyperglycemia in both the lived and died groups was infection (43% versus 55%). There were no significant trends for mortality related to the degree of hyperglycemia, number of risk factors for hyperglycemia, or number of episodes of hyperglycemia.

The hyperglycemic patients with a history of diabetes were younger than the nondiabetics (55.6 ± 2.2 years vs 66.5 ± 4.6 years, $p 0.047$) but did not differ in any of the laboratory values measured. Steroid administration was significantly higher as a risk factor (38% vs 9%, $p 0.001$) and a more frequent cause (38% vs 3%, $p 0.0001$) of hyperglycemia in hyperglycemic patients who did have diabetes than in those who did not. The most common cause of hyperglycemia in patients with diabetes was infection (53%). In contrast, infection was not a cause of hyperglycemia in any of the nondiabetic patients.

Mortality. A total of 5351 patients were admitted to The Mount Sinai Hospital during the period of this study who did not have laboratory values falling into the ranges we defined for hypoglycemia and severe hyperglycemia. Of these 5351 patients, only 2.3% (125/5351) died. The mortality rates for the hypoglycemic and hyperglycemic groups were highly and significantly different ($p < 0.0001$) from that of patients with a blood glucose level between 2.8 and 22.1 mmol/L (50 mg/dL – 399 mg/dL) (22.2%, 11.1%, 2.3%, respectively). Consequently, the relative risk of mortality for a hospitalized patient who had hypoglycemia or marked hyperglycemia during the period of this study was 9.7 and 4.8 respectively.

Conclusions

The present study is the first prospective evaluation of the incidence and outcome of all patients having either hypoglycemia or marked hyperglycemia during hospitalization in a tertiary-care medical center. Our major finding was that mortality during hospitalization was vastly and

significantly increased in both groups of patients. Patients who were hypoglycemic had a relative risk of dying during their hospitalization of 9.7. Patients with a blood glucose elevation of 22.2 mmol/L (400 mg/dL) or higher had a relative risk of mortality of 4.8. However, neither hypoglycemia nor hyperglycemia was the immediate cause of death in any patient. Furthermore, mortality rates of the hypoglycemic and hyperglycemic patients were not influenced by prior history of diabetes. Consequently, marked hyperglycemia and hypoglycemia are metabolic markers of patients at high risk for in-hospital mortality and reflect the severity of underlying disease processes.

The only previous study investigating hypoglycemia in hospitalized patients reported an incidence of hypoglycemia of 1.2% (1). This is similar to the rate of 1.5% in the present study. The previously reported mortality rate of 27% for patients with a hypoglycemic episode is also similar to the mortality rate of 22% among hypoglycemic patients in the present study. There are no earlier reports of studies examining the incidence or potential relationship to mortality of marked hyperglycemia during hospitalization.

Hypoglycemia was found in 1.5% of all hospital admissions. The majority of the cases occurred in patients without diabetes. This reflects the importance of diseases other than diabetes in the pathogenesis of hypoglycemia in hospitalized patients. Hypoglycemic patients who died had more serious underlying disorders than those who survived hospitalization, as reflected by their significantly increased white blood cell counts, decreased hematocrits, and multiple risk factors, including sepsis, cancer, and renal insufficiency. Our observations confirm prior studies which have shown that sepsis (3) and renal insufficiency (4–6) can result in hypoglycemia, even in individuals without a history of diabetes. Consequently, patients with malignancy, renal insufficiency, or severe infection who are hypoglycemic on hospital admission are at high risk for a poor hospital outcome. Such patients should be identified, treated aggressively for their underlying disease, and monitored closely. In addition, when unexplained hypoglycemia develops in patients during hospitalization, potentially life-threatening causes such as sepsis should be aggressively sought and treated.

The elevated creatinine levels of the black hypoglycemic patients in this study may have reflected greater severity of underlying illness in these patients, which might explain their increased mortality. However, the group of His-

panic hypoglycemic patients also had an increased mortality rate, yet had laboratory parameters similar to and were younger (although not significantly) than their white counterparts in the study. Epidemiologic studies have also shown a higher mortality rate for Hispanic patients (7). Additionally, Rogers found that black patients have a threefold higher mortality due to diabetes than do white patients (8), and McCord and Freeman found excess mortality secondary to diabetes in Harlem (9). The present study confirms the findings of an increased mortality rate in black and Hispanic populations specifically utilizing hypoglycemia as a risk factor for in-hospital mortality. Further investigations are required in order to implement effective intervention, treatment, and preventive strategies.

Severe hyperglycemia was found in patients who did and did not have a history of diabetes. The stress and severity of the underlying illness, along with the attendant increase in catecholamines, resulted in hyperglycemia in patients without a prior history of diabetes. Steroids had been administered to many of the nondiabetic patients who developed severe hyperglycemia, confirming the powerful impact that steroids have on glucose homeostasis. Among patients with previously diagnosed diabetes, the majority were infected, providing further evidence for the marked insulin resistance that accompanies stress and infection in individuals with diabetes. In contrast to the hypoglycemic patients, among the hyperglycemic group mortality did not differ by ethnicity. Hyperglycemic patients who died were older and more likely to have cancer than hyperglycemic patients who survived.

In conclusion, we found that hypoglycemia or severe hyperglycemia occurs in approximately 3% of hospitalized patients. Both hypoglycemia and marked hyperglycemia are associated with highly significant increases in mortality and serve as indicators for patients at risk of dying during their hospitalization. The majority of the

patients who died were not patients known to have diabetes, further identifying the hypoglycemic and hyperglycemic patients at greatest risk.

Further studies are needed to determine the pathophysiology of the hypoglycemia and marked hyperglycemia that were exhibited by these patients. Our documentation of the increased mortality of hospitalized patients with hypoglycemia and severe hyperglycemia should alert physicians to patients who are at high risk for in-hospital mortality. Early identification may be particularly important for black and Hispanic patients. Further studies will determine if early and aggressive treatment of underlying reversible disorders in patients with hypoglycemia and severe hyperglycemia will result in decreased mortality rates.

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Pharmaceutical Industry Support for Continuing Medical Education Programs:

A Review of Current Ethical Guidelines

FRED ROSNER, M.D., F.A.C.P.

Abstract

Ethical relationships between physicians and the drug industry require guidelines to maintain the integrity of the medical profession. The acceptance of gifts and subsidies for the cost of continuing-medical-education conferences is considered ethically acceptable provided the gifts are of minimal value and that the control of content and the selection of presenters and moderators for industry-supported CME programs rest solely with the CME-sponsoring institution. Current ethical guidelines for pharmaceutical industry support of CME programs are reviewed in this essay.

THE PHARMACEUTICAL INDUSTRY is one of the major sources of financial support for continuing medical education programs. Criticism has been voiced against some of the interactions between that industry and physicians. The integrity of the medical profession and public trust in physicians have suffered from the lavish gifts, fees, hospitality, and support of education and clinical trials that the drug industry provides to physicians and academicians.

I have previously written about the ethics of accepting free gifts at medical conventions (1). Some authors decry the pharmaceutical company promotions at house staff educational luncheons and other gifts that are considered to be "buying goodwill" (2). The relationship of drug promotion

to the clinical investigator and to scientific exchange was addressed by the Commissioner of the Food and Drug Administration (3).

Recently, guidelines have been developed to control these interactions and keep them within ethically acceptable bounds. This paper discusses the funding of continuing medical education by the pharmaceutical industry and reviews the ethical guidelines developed to define the proper relationship between physicians and the drug industry.

Drug Companies and the Funding of Continuing Medical Education

The relationship between the pharmaceutical industry and the medical profession in the funding of continuing medical education (CME) has been the subject of some concern to many groups and individuals involved in medical education and medical journalism. Distinctions between advertising, promotion, information, and education are blurred. CME for physicians cannot and should not come exclusively from drug company representatives, many of whom are medically unqualified and whose activities are uncon-

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From the Departments of Medicine at Mount Sinai Services at Queens Hospital Center, and Mount Sinai School of Medicine (CUNY), New York. Address reprint requests to Fred Rosner, M.D., F.A.C.P., Director, Department of Medicine, Queens Hospital Center, 82-68 164th Street, Jamaica, NY 11432.

trolled and unscrutinized by independent sources (4).

Drug companies' gifts to benefit patients, medical libraries, medical research, medical education, resident education, or travel, if administered by hospitals or universities, can be accepted with appreciation (5). Is it ethical, however, for a drug company to sponsor lavish social affairs associated with CME activities? No doubt some CME activities would cease or perish without "the social glitz provided by drug company money" (6).

Estimates of the annual expenditures by drug companies for CME range from \$2.5 billion to \$10 billion. Not only do pharmaceutical houses spend large sums of money to "educate" physicians at CME events, they also offer large honoraria to leading medical academicians for lectures. Many CME courses occur at ski resorts and golf clubs, and on luxury cruise liners.

Some CME providers are concerned that the marketing objectives of the pharmaceutical companies are adversely affecting the scientific quality of some CME programs.

Drug Industry Contributions To Medical Care

To present a balanced picture, I should point out that major contributions to medical care have been made by the pharmaceutical industry. Through advertising, symposia, and professional representatives, the industry has changed medical practice in beneficial ways and greatly helped patients by urging physicians to change from outdated methods and treatment to more effective and safe new therapies. Physicians, in many cases, are not adequately informed of some of the benefits of newer therapy. In fact, the efforts of the pharmaceutical companies have assisted in this effort. Because the pharmaceutical industry has been, in almost all cases, the originator of new drugs and vaccines, it has an obligation—through publications, scientific meetings, promotional materials, and representatives—to inform the medical profession about the benefits and risks of the newer advances in therapeutics. Such information is important with respect to patient care.

Ethical Guidelines

The medical community has recently developed guidelines for ethical conduct of physicians vis-à-vis the pharmaceutical industry.

World Health Organization. The World Health Organization states that in symposia sponsored by a pharmaceutical manufacturer or

distributor, objective scientific content should be paramount. Entertainment or other hospitality and any gifts offered to physicians should be secondary to the main purpose of the meeting and should be kept to a modest level. Any support to physicians to participate in domestic or international symposia should not be conditional on any obligation to use or promote any medicinal product (7).

United Kingdom. In the United Kingdom, the British Medical Association *Handbook of Medical Ethics* (8) states that:

Gifts in the form of articles designed as promotional aids, whether related to a particular product or of general utility, may be distributed to members of the medical and allied professions provided the gift is inexpensive and relevant to the practice of medicine or pharmacy.

Because of "increasing concern in recent years about the relationship between doctors and the pharmaceutical industry," Britain's Royal College of Physicians assembled a working party to examine the issue and to make recommendations. Its report addresses the issues of drug company support of CME; hospitality, gifts, payments, and investments; research projects and clinical trials; and disclosure of interest and publishing. The report (8) concludes as follows:

We recommend that Fellows and Members of the College ensure that their behaviour in relation to the pharmaceutical industry is always seen to be scrupulously impartial and honest. The overriding principle is that any benefit in cash or kind, any gift, any hospitality or any subsidy received from a pharmaceutical company must leave the doctor's independence of judgement manifestly unimpaired. When it comes to the margin between what is acceptable and what is unacceptable, judgement may sometimes be difficult: a useful criterion of acceptability may be "would you be willing to have these arrangements generally known?"

The report was criticized for producing a code full of words like "acceptable," "moderate," "reasonable," "relevant," and "appropriate" (9). A weekend in Spain to hear about the benefits of a new tranquilizer might seem quite "reasonable" to one physician, whereas a ballpoint pen advertising a diuretic may seem "unreasonable" to another.

United States. In the United States, the Accreditation Council for Continuing Medical Education (ACCME) adopted guidelines for commercial support of continuing medical education in June 1984. These guidelines are periodically reviewed. During the 1990 review, a number of suggestions for change were made; the revised guidelines were adopted by ACCME on March 16, 1991 and took effect May 11, 1991. Minor additional

revisions have since been made (10). The ACCME guidelines state that accredited CME sponsors are responsible for the funding, content, quality, and scientific integrity of all CME activities certified for credit. Funds from a commercial source should be in the form of an educational grant made payable to the accredited sponsor for the support of programming. Payment of reasonable honoraria is customary and proper. Commercial support must be acknowledged in printed announcements and brochures. Commercially supported social events at CME activities should not compete with, nor take precedence over, the educational events. It is not permissible to provide for attendees' travel, lodging, honoraria, or personal expenses.

These ACCME guidelines were adopted by the Medical Society of the State of New York in its CME accreditation process (11).

The Accreditation Council for Medical Education (ACME) in January 1983 adopted a set of guidelines for industry-professional relationships that addresses the issues of program control, roles for industry and recognition of their support, and a code of conduct for exhibitors.

The Society of Medical School Directors of CME unanimously adopted the following guidelines on the relationship between commercial companies and CME courses presented by medical schools:

1. Medical schools should not present or cosponsor a continuing education course concentrating on products of a commercial company that is providing financial support for that course unless the pertinent alternatives to those products are also presented.
2. Medical schools should not present or cosponsor a continuing education course that is planned and/or implemented through an advertising or other intermediary firm employed by a commercial company.
3. Medical schools should exert substantial caution before agreeing to sponsor or cosponsor a continuing education course that is distributed by a commercial company. If the course is a correspondence course utilizing only bound books, the consistency of the content can be more assured than in those instances when "live" discussions are included.
4. All money from commercial companies to support CME courses presented by medical schools should be paid to the respective school and handled in accordance with institutional policies.

The American Medical Association (AMA), in its 1992 edition of *Code of Medical Ethics: Current Opinions*, states that a physician should not be influenced in the prescribing of drugs, devices, or appliances by a direct or indirect financial interest in a pharmaceutical firm or other supplier (12). The American College of Physicians also published a statement in its *Ethics Manual* about physicians avoiding any business arrangement

that might, because of personal gain, influence their decisions about patient care (13).

Other medical groups have drafted position papers or guidelines on the relationship between physicians and the pharmaceutical industry. These include the American Surgical Association, the American College of Obstetricians and Gynecologists, the American College of Cardiology, the American Academy of Ophthalmology, the Infectious Diseases Society of America, the Canadian Medical Association, and the Royal Australian College of Physicians.

The guidelines of the American College of Physicians (ACP), adopted in September 1989 (14), include four position statements:

Position 1

Gifts, hospitality, or subsidies offered to physicians by the pharmaceutical industry ought not to be accepted if acceptance might influence or appear to others to influence the objectivity of clinical judgment. A useful criterion in determining acceptable activities and relationships is: Would you be willing to have these arrangements generally known?

Position 2

Independent institutional and organizational continuing medical education providers that accept industry supported programs should develop and enforce explicit policies to maintain complete control of program content.

Position 3

Professional societies should develop and promulgate guidelines that discourage excessive industry-sponsored gifts, amenities, and hospitality to physicians at meetings.

Position 4

Physicians who participate in practice-based trials of pharmaceuticals should conduct their activities in accord with basic precepts of accepted scientific methodology.

The four position statements of the ACP were unanimously endorsed by the Pharmaceutical Manufacturers Association in May 1990. On December 3, 1990, the Council on Ethical and Judicial Affairs of the AMA issued an opinion on gifts to physicians from industry (15). The unacceptable gifts include cash subsidies for physicians attending meetings, payment for token consulting or advisory services, and gifts with "strings attached." Acceptable gifts include textbooks, work-related gifts of minimal value such as pens, note pads, and penlights, subsidies for the cost of CME conferences, scholarships for medical students and house officers, reasonable compensation for consultants, and modest meals in conjunction with CME programs.

The Pharmaceutical Manufacturers Association (PMA) issued the pamphlet "Code of Pharmaceutical Marketing Practices" embodying the AMA guidelines (16). Perhaps by coincidence, both the AMA and PMA attestations were issued

just a few days before December 11, 1990, when Senator Edward Kennedy chaired Senate hearings on promotional practices in the pharmaceutical industry. The AMA Residents Physician Section also adopted these guidelines (17). Some physicians criticize these guidelines, which allow gifts to physicians from industry, as posing risks to the integrity of the medical profession (18). The guidelines, however, carefully balance the benefits and risks of gifts from industry and eliminate abusive promotional practices (19).

On November 27, 1992, the Food and Drug Administration of the U.S. Department of Health and Human Services published its draft policy statement on industry-supported scientific and educational activities (20). The statement describes categories of educational activities that may continue to be funded by industry and yet avoid regulation as advertising or promotional labeling. Included are guidelines for control of content and selection of presenters and moderators for industry-supported CME programs, disclosure of financial relationships, and ancillary promotional activities. The statement concludes with the assertion that the FDA "will seek to rely to the extent possible on major accrediting organizations [such as ACCME] to monitor company-supported educational activities conducted by their accredited providers and ensure that such activities are independent and nonpromotional."

Canada. In 1994, the Canadian Medical Association issued an update of its policy concerning physicians and the pharmaceutical industry (21). In regard to CME specifically, the guidelines require, among other things, that the ultimate decision on the organization, content, funding arrangements, and choice of CME activities shall lie in the hands of the physician organizers; that CME organizers should not have conflicts of interest by virtue of relationships with the company funding the CME activity; and that funds should be in the form of an educational grant payable to the institution sponsoring the CME activity.

Conclusions

In the past several years the AMA, the BMA, the CMA, the ACCME, the ACP, the FDA, and other organizations have adopted and published guidelines defining some of the ethical relationships between drug companies and the medical profession, particularly in relation to CME. The common features of nearly all the guidelines are that CME sponsors, not the drug industry or the funding source, should be responsible for the content and quality of the CME program, that the

funds should be given in the form of an unrestricted educational grant to the CME sponsoring organization, and that financial arrangements and any possible conflict of interest be disclosed. It now remains to be seen whether advisory guidelines will be followed by both concerned parties.

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Pelvic Exenteration in Gynecologic Oncology:

Experience at The Mount Sinai Medical Center, 1975–1992

PETER R. DOTTINO, M.D., RUDY A. SEGNA, M.D., T. SCOTT JENNINGS, M.D., JOHN P. MANDELI, PH.D.,
KENNETH KONSKE, M.D., AND CARMEL J. COHEN, M.D.

Abstract

Thirty-nine patients underwent pelvic exenteration for gynecologic malignancies at The Mount Sinai Medical Center between 1975 and 1992. Surgical techniques, morbidity, survival, and other variables for patients so treated in two periods, 1975–1984 and 1985–1992, were compared. The primary cancer included squamous cell carcinoma of the cervix, 27; adenocarcinoma of the cervix, 1; squamous cell carcinoma of the vagina, 4; adenocarcinoma of the endometrium, 4; squamous cell carcinoma of the vulva, 2; and adenocarcinoma of the rectum, 1. Median survival was 23.1 months, with a median follow-up of 18 months. Survival was significantly related to status of the lymph nodes (p 0.0004) and surgical margins (p 0.0038). There were two postoperative mortalities, one due to pulmonary embolus and another to myocardial infarction. The ability in the second period analyzed, 1985–1992, to integrate a continent urinary reservoir and supravaginal exenteration without colostomy yet not induce increased morbidity or decreased survival, has not been previously reported.

PELVIC EXENTERATION is a radical surgical procedure, primarily for recurrent gynecologic malignancy, to remove the uterus, cervix, vagina, parametria, bladder, and rectosigmoid colon in female patients that was first described by Brunschwig over 45 years ago (1). Considerable controversy has surrounded this procedure due to the high perioperative morbidity as well as the potential psychosocial impact of impaired gastrointestinal, urologic, and sexual functioning on the patient. In addition, it has been difficult to improve on the poor prognosis of patients found to have recurrent

neoplasms of the genital tract, and patient survival has not justified the procedure in the eyes of some investigators. However, with improvements in perioperative care, surgical techniques, and patient selection, pelvic exenteration has gradually evolved into a procedure with acceptable morbidity, therapeutic efficacy, and lessened functional loss for the majority of patients with recurrent pelvic cancer.

This report spans 17 years and includes 39 pelvic exenterations performed at The Mount Sinai Medical Center by the Division of Gynecologic Oncology for recurrent pelvic cancer. We explore the modifications that have taken place over these years as well as the survival, morbidity and mortality, and prognostic variables associated with the surgical undertaking.

Materials and Methods

The records of 39 patients who underwent pelvic exenteration by the Division of Gynecologic Oncology at The Mount Sinai Medical Cen-

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From the Department of Obstetrics, Gynecology and Reproductive Sciences, Division of Gynecologic Oncology, and the Department of Biomathematical Sciences (JPM), The Mount Sinai Medical Center, New York, NY. Address reprint requests to Carmel J. Cohen, M.D., Box 1173, Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029.

TABLE 1
Site and Histologic Diagnosis, 39 Patients Undergoing Exenteration

Type	No.	%
Cervix		
Squamous cell (27)	28	71.8
Adenocarcinoma (1)		
Vagina	4	10.3
Squamous cell (4)		
Endometrial	4	10.3
Adenocarcinoma (4)		
Vulva	2	5.1
Squamous cell (2)		
Rectum	1	2.6
Adenocarcinoma (1)		
Total	39	100

TABLE 2
Median Survival, 39 Patients Undergoing Exenteration

Variable	Median survival (mos)	p
Initial treatment		NS
None (11/39)	28.8	
RT only (12/39)	19.4	
RT + surgery (16/39)	22.2	
Time to recurrence		NS
>5 years (7/39)	29.9	
1–5 years (13/39)	22.2	
<1 years (19/39)	23.1	
Chemotherapy prior to exenteration		NS
Yes 12/39	23.1	
No 27/39	28.0	
Type of exenteration		NS
Anterior (11/39)	31.1	
Posterior (5/39)	16.2	
Total (23/39)	22.2	
Type of total pelvic exenteration		NS
Infralevator (12/39)	9.9	
Supralevator (11/39)	15.1	
Nodal status		0.0004
Negative (26/39)	31.1	
Positive (13/39)	6.6	
Surgical margins		0.0038
Negative (31/39)	31.1	
Positive (8/39)	8.9	
Overall (39 patients)	23.1	

NS, not significant ($p = 0.05$); RT, radiotherapy.

ter between 1975 and 1992 were reviewed. Patients were considered candidates for the procedure if determined to have pelvic recurrence of predominantly gynecologic malignancies, or to require primary procedures for stage IVa carcinoma of the cervix or vagina metastatic to the

bladder or rectal mucosa; one patient with a central pelvic recurrence from adenocarcinoma of the rectum was included. Any patient with evidence of extrapelvic metastases, ascites, or lateral pelvic disease was not surgically explored for exenteration. In addition, some patients found during surgical exploration to have previously unsuspected evidence of malignant ascites or macroscopic extrapelvic or omental disease did not undergo resection.

Standard definitions of pelvic exenterative procedures were used in this study: anterior exenteration included en bloc removal of the uterus, cervix, parametria, and vagina and its supporting tissues as well as the bladder and pelvic ureters; posterior exenteration was defined as en bloc resection of the pelvic viscera with the rectosigmoid colon; total exenteration included en bloc resection of all of these organs and supporting structures; supralevator exenteration was treated as a subgroup defining resection at or above the level of the levator muscles; infralevator exenterative procedures included resection of the levator muscles, urogenital diaphragm, and vulvoperineal tissues (2).

The primary site and histologic type of the cancer were determined retrospectively for all patients, along with initial therapy and type of exenteration. Time to recurrence was defined as the interval from the initial therapy to the date of exenteration. Major changes in surgical technique over the years—defined as type of urinary diversion utilized and the degree of rectal resection performed—were also analyzed. Morbidity was also analyzed, categorized as early morbid events occurring prior to discharge and late complications occurring after discharge from the hospital. Many aspects of the exenterations performed were analyzed by period performed, 1975–1984 or 1985–1992. Potential prognostic variables were determined by chi-square test. Survival curves were generated using the Kaplan-Meier method. The generalized Wilcoxon two-sample test was used to determine statistical differences in survival.

Results

Among the 39 patients whose records were reviewed, 11 anterior, 5 posterior, and 23 total exenterations were performed. The cancer sites and histologic diagnoses are summarized in Table 1. The age of the patients ranged from 32 to 84 years, median 56 years. The median overall survival was 23.1 months (Fig.). Survival in several subgroups of patients (Table 2) and time periods

(Table 3) was compared. The only statistically significant variables having an impact on survival were status of the lymph nodes and surgical margins (Fig. 1). There were two postoperative deaths (5%), both in the earlier pre-1984 series of patients, one due to pulmonary embolus and one due to myocardial infarction. The morbid events are outlined in Table 4. Morbidity was compared in several subgroups of patients and reported as a ratio of a number of morbid events per patient (Table 5). There were no statistically significant differences in morbidity by date or by type of exenteration (infralevator or supralelevator) performed. It appears that patients undergoing posterior exenteration did experience more morbidity. Those patients undergoing primary exenteration had less morbidity than patients who were previously treated with radiation, surgery, or both.

During the time covered by this study, many surgical innovations were introduced, and by 1985 had been readily adopted to radical pelvic surgery, including pelvic exenteration. Of particular significance were three innovations that had a direct impact on the performance of pelvic exenteration: the use of automated surgical staplers to divide and reanastomose bowel segments; the construction of continent urinary reservoirs instead of urinary diversion; and the favoring of supralelevator over infralevator exenteration to preserve the perineal floor and avoid permanent colostomy. To analyse the effect of integration of these surgical innovations, we compared a number of variables in patients undergoing exenteration in the period 1975–1984 and in the period 1985–1992 (Table 3). Operative time was significantly less in the patients undergoing exenteration in the later period, but there was no significant difference in hospital stay, blood loss, morbidity, or survival.

Discussion

Brunschwig first described pelvic exenteration for the treatment of pelvic malignancies in 1948 (1). The mortality rate at that time was 20%, and the only contraindication to performing the procedure was the presence of macroscopic metastatic disease outside the pelvis. As the procedure has evolved over the years, operative mortality has fallen to $\leq 5\%$ and 5-year survival rates as high as 60% have been reported (3–8). This improved survival and decreased morbidity are the result of a number of factors, including improved patient selection, improved surgical techniques and instrumentation, use of antimicrobial ther-

TABLE 3
Historical Comparison, 39 Patients Undergoing Exenteration

Variable	1975–1984 N = 20	1985–1992 N = 19
Length of stay, median days	35 (3–187)	34 (15–130)
Blood loss, median mL	2447 (1000–7000)	2505 (1000–7000)
OR time, median min	735 (415–820)	473 (300–790)
Transfusion, units	5 (3–20)	5 (3–13)
Fluid requirement, median mL	7100 (1500–14000)	10000 (5500–20000)
SICU stay, median days	5 (0–12)	3 (0–5)
Total parenteral nutrition, N	5	4
Swan-Ganz catheter, N	6	7
Morbidity, (no. morbid events/pt)	2.4	2.1
Survival, median mos.	23.8	23.1
Supralelevator TPE, N	0	11
Continent urinary pouch, N	0	11
Ileal conduit, N	15	7
Colon conduit, N	1	0

TABLE 4
Complications of Pelvic Exenteration, 39 Patients

Complications	Total (%) N = 87	Early (%) N = 45	Late (%) N = 42
Sepsis	14 (16)	7 (16)	7 (17)
Wound infection	8 (9)	8 (18)	0
Pleural effusion	7 (8)	3 (7)	4 (10)
Intraoperative injury	6 (7)	6 (14)	0
Small bowel obstruction	6 (7)	1 (<5)	5 (12)
Deep venous thrombosis	5 (6)	1 (<5)	4 (10)
Vesico/rectovaginal fistula	4 (5)	2 (<5)	2 (<5)
Abscess	3 (<5)	2 (<5)	1 (<5)
Hemorrhage	3 (<5)	1 (<5)	2 (<5)
Pneumonia	3 (<5)	2 (<5)	1 (<5)
Ureteral stricture	3 (<5)	0	3 (7)
Ureteral leak	3 (<5)	2 (<5)	1 (<5)
Perineal hernia	3 (<5)	0	3 (7)
Sloughing of ileal conduit	3 (<5)	0	3 (7)
Short bowel syndrome	2 (<5)	1 (<5)	1 (<5)
Enteroperitoneal fistula	2 (<5)	1 (<5)	1 (<5)
Ureteroperitoneal fistula	2 (<5)	1 (<5)	1 (<5)
Pulmonary embolus	2 (<5)	2 (<5)	0
Cardiac arrest	2 (<5)	1 (<5)	1 (<5)
Arrhythmias	2 (<5)	2 (<5)	0
Enterocutaneous fistula	1 (<5)	0	1 (<5)
Arterial thrombus	1 (<5)	1 (<5)	0
Stomal stenosis/prolapse	1 (<5)	0	1 (<5)
Wound dehiscence	1 (<5)	1 (<5)	0

apy, and improved preoperative and postoperative care (6).

As previously reported, the presence of disease metastatic to lymph nodes and positive surgical margins are strong prognostic indicators in patients undergoing exenteration (4, 6, 7). In this series, patients with positive lymph nodes had a median survival of 6.6 months, as opposed to 31.1 months in those with negative nodes ($p = 0.0004$,

TABLE 5
Morbidity Assessment, 39 Patients Undergoing Exenteration
(No. of Morbid Events per Patient)

Variable	No.
Type of exenteration	
Anterior	1.7
Posterior	3.8
Total	2.1
Time period	
1975–1984	2.4
1985–1992	2.1
Type of TPE	
Infralevator	2.2
Supralevator	2.1
Prior treatment	
None	1.5
RT only	2.5
RT + surgery	2.6

TPE, total pelvic exenteration; RT, radiotherapy.

Fig.). These results are similar to those of Morley (3, 4): no patient with metastases to lymph nodes survived five years, whereas 70% of patients with negative nodes survived five years (7). Patients with positive surgical margins had a median survival of 8.9 months, and those with negative margins had a 31.1-month median survival ($p = 0.0038$). The impact of tumor in surgical margins in these patients is similar to that described by Shingleton et al.: surgical margins were the most important determinants of survival (7). The type of exenteration, prior treatment, and time interval from original diagnosis to time of exenteration did not have an impact on survival in our study.

The degree of morbidity for this operation reported here is similar to that described in a number of previous studies (2–5, 7). A variety of morbid events occurred in the patients reported on here (Tables 4, 5). Despite surgical advances over the years, the morbidity rate is still impressive and essentially unchanged, a result confirmed by other studies (3). Our series reports two postoperative mortalities, an incidence of 5%, comparable to that in other series. As in Soper's report from Duke University, complications appear to be higher in those patients undergoing exenteration following pelvic irradiation than in those not irradiated (5). Unlike Soper's results, however, our data contain no evidence of reduced perioperative morbidity during the period in which surgical innovations were introduced to the procedure. This may be due to patient selection, or to the fact that the patients at Duke University continued to undergo simple urinary diversion without construction of continent reservoirs, which may have par-

tially alleviated some immediate postoperative complications in these patients.

The adoption of supralevator exenterative procedures appears to have lessened the functional impairment by obviating the need for sigmoid colostomy in a large percentage of women undergoing this procedure, without an adverse impact on survival or an increase in perioperative morbidity. The continent urinary diversion also appears to improve patient acceptance without affecting length of survival (9). The application of automated surgical staplers to the patient undergoing exenteration has significantly decreased operative times improving surgeon acceptance of the procedure (Tables 2, 5).

Vera and others investigated the subjective responses of women undergoing pelvic exenteration for recurrent pelvic malignancy, reporting in 1981 that only 2 of 21 patients had an unfavorable subjective adjustment to exenteration with colostomy and urinary diversion; most patients saw their quality of life as superior to that recalled prior to the exenterative procedure (10). This study, as well as others (11, 12), suggests that patients can adjust to the degree of functional impairment imposed by pelvic exenteration. An important finding by Vera was that bowel and urinary stomas were the source of the most difficult postoperative adjustment; over one-quarter of these patients continued to find stoma care to be the most disruptive effect of exenteration for a median of four years after surgery. The innovations described in the present study illustrate potential advantages offered in selected patients undergoing total pelvic exenteration today.

Miller and colleagues reported that in 28% of women undergoing exploration for possible exenteration, those surgical plans were abandoned due to intraoperative findings (13). In their series, over 80% of the procedures were abandoned either because of gross intraperitoneal disease or because of metastatic nodal disease. Since many of these occult metastases can be detected laparoscopically, we have aggressively utilized operative laparoscopy since 1992 in an attempt to determine resectability prior to the performance of laparotomy (14).

Through the continued efforts of pelvic surgeons to apply innovations in surgical technique and patient care, pelvic exenteration remains a viable treatment option with acceptable mortality and manageable morbidity for women with recurrent gynecologic malignancy. Although not all women explored for possible exenteration will be found to be candidates for the procedure, most

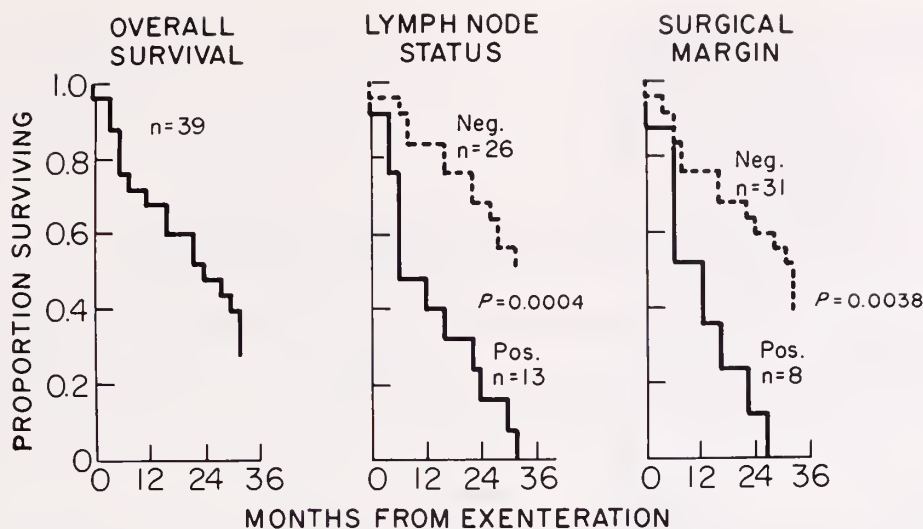


Fig.

can receive effective extirpative procedures with less functional impairment than similar patients ten or more years ago. Because of the therapeutic efficacy of this operation and its excellent functional results, it should not be viewed as a last attempt to salvage patients with advanced or recurrent central pelvic cancer, but instead as a viable treatment modality for the management of women with gynecologic malignancies.

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Central Neurocytoma:

An Unusual Intraventricular Tumor

SUSAN P. MOLINARI, M.D., KUMARASWAMY SIVAKUMAR, M.B.B.S., MRCP, DAVID CORBIN, M.B.B.S., MRCP, AND MELVIN D. YAHR, M.D.

Abstract

A case of central neurocytoma occurring in a 22-year-old man is presented. This tumor is generally considered to be benign in appearance, nonrecurrent, and amenable to surgical resection. However, this particular neurocytoma demonstrated anaplastic features, raising the issue of malignancy and the need for additional modes of treatment. Implicated factors and possible optimal treatment for this tumor are discussed.

CENTRAL NEUROCYTOMA is an unusual intraventricular tumor of neuronal origin only recently recognized and reported by Hassoun et al. (1). It has to date primarily been noted in young adults. Initial clinical appearance is similar to that of other intraventricular tumors, with signs and symptoms of increased intracranial pressure. Because of their location and radiologic and histologic appearance, neurocytomas have been mistaken for oligodendrogliomas, ependymomas, and other rare intraventricular tumors. The diagnosis is established histologically by the finding of neuronal differentiation on electron microscopy and the presence of neuronal markers in immunohistochemical studies. Although this tumor is considered to be benign, its natural history has not been fully defined. We report a case of central neurocytoma located within the lateral and third ventricle, displaying areas of focal necroses and rare mitotic figures. These features are atypical for neurocytomas and may have implications for its exact nature and mode of treatment.

Case Report

A 22-year-old male native of Barbados was examined for further evaluation of an eight-month history of headaches. The headaches were episodic, with acute onset, often associated with nausea, vomiting, and photophobia. Valsalva maneuvers exacerbated the headaches. The patient discovered that lying prone with his head elevated on a pillow offered maximal relief. Neurologic examination revealed minimal right-sided findings limited to a flattened nasolabial fold, a mild pronator drift, and slowed rapid sequential movements. A CT scan (Fig.) demonstrated a predominantly isodense mass measuring 2×2 cm located in the left lateral ventricle near the foramen of Monro extending into the third ventricle. Calcifications were present in the mass. MRI T1-weighted images revealed an iso-intense mass containing small hypo-intense signals representing calcifications. Cerebral angiography revealed a relatively avascular intraventricular tumor. At surgery, the tumor was described as a tan, friable mass invading the wall of the left lateral ventricle extending into the third ventricular side of the foramen of Monro. A complete resection of the tumor was carried out.

Histologic preparations revealed a neoplasm growing in reticulin-free sheets with occasional neuroblastic rosettes. Cells with uniform nuclei and scanty amphophilic cytoplasm were present.

From the Department of Neurology (SPM, KS, MDY), The Mount Sinai Medical Center, New York, NY, and the Department of Neurology (DC), Queen Elizabeth Hospital, Bridgetown, St. Michael, Barbados. Address correspondence and reprint requests to Melvin D. Yahr, M.D., Mount Sinai Medical Center, Department of Neurology, Box 1139, One Gustave L. Levy Place, New York, NY 10029-6574.

Areas of necrosis and scattered mitotic figures were evident, but no microvascular proliferation was seen. Tumor cell cytoplasm reacted with peroxidase-linked antibodies against neuron-specific enolase and synaptophysin, but not against glial fibrillary acidic protein, neurofilament, or S-100 antigen. Tumor cell cytoplasm was not argyrophilic. Electron microscopy revealed microtubule-rich cell processes verifying the presence of neuronal differentiation. These findings combined with the absence of ependymal and oligodendrocytic differentiation established the diagnosis of neurocytoma.

At 24-month follow-up, the patient remained symptom free without evidence of recurrence on CT scan.

Discussion

Central neurocytoma, also referred to as intraventricular neurocytoma, is primarily located in the lateral or third ventricle near the foramen of Monro. Tumors in this region are relatively infrequent and are estimated to represent 6% of all cerebral tumors (2).

Initial symptoms are increasing intracranial pressure due to obstructive hydrocephalus and intermittent obstruction of the third ventricular cavity. The symptoms of intermittent obstruction usually arise suddenly, especially with positional change such as forward bending. Maneuvers that increase intracranial pressure, such as coughing, sneezing, or straining, will also often produce symptoms, headache being the most prominent. Headache is intense, with postural onset, and is frequently associated with nausea and vomiting. The patient often discovers that relief is obtained from repositioning the head. Other symptoms due to obstructive hydrocephalus, including confusion, apathy, decreased visual acuity, and blurring of vision, may also be present. However, asymptomatic cases of neurocytoma have been discovered as incidental findings on CT scans taken after minor head trauma (3).

On CT scan, central neurocytomas are not distinguishable from other tumors located in this region, such as meningiomas, oligodendrogliomas, ependymomas, choroid plexus papillomas, and colloid cysts (4, 5). MRIs are useful for better definition of the extent of the tumor, but do not aid in the differential diagnosis of tumors in this location (4, 6).

Pathologically, neurocytomas can be mistaken for oligodendrogliomas and ependymomas (1, 3, 7, 8). The appearance on microscopy can mimic the "clear cells" of oligodendrogliomas and

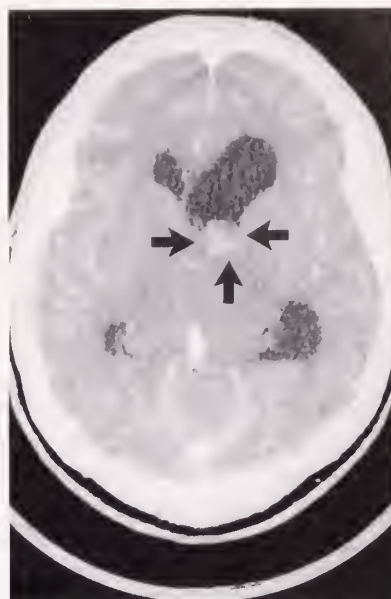


Fig. CT scan showing tumor in left lateral ventricle obstructing foramen of Monro and extending into third ventricle.

the rosettes of ependymomas and have been mistaken for these tumors (6, 8, 10). Electron microscopy and immunohistochemical staining now make it possible to differentiate neurocytomas from other tumors. Ultrastructural characteristics demonstrate features of neuronal differentiation, such as synapses, axons, or neurosecretory granules (1, 3–5, 8, 10). Immunohistochemical studies of neurocytomas have shown expression of several neuronal markers, including synaptophysin, neuron-specific enolase, S-100 protein, glial fibrillary acidic protein, Leu-7, and neurofilament proteins. Synaptophysin, a glycoprotein component of presynaptic vesicle membranes, is considered specific for neurocytomas (10, 11).

Neurocytomas are considered benign tumors. However, there are reported cases of "anaplastic" neurocytomas (5, 10, 12). Histologically, these cases display high degrees of mitoses and necroses and variable degrees of microvascular proliferation.

Treatment has included resection of the tumor and radiation therapy. In a retrospective study, six cases initially diagnosed as intraventricular oligodendrogliomas between 1968 and 1985 were found to be neurocytomas (3). The surgical material was reexamined histologically, with immunohistochemical studies and electron microscopy, which established their nature. All six cases had surgical resection of the neurocytoma; partial in three and total in three. Five of these six patients received postoperative radiation and are without recurrence in follow-up up to

19 years. The sixth patient underwent complete resection without postoperative radiation and is also without recurrence 56 months after treatment. Hence this retrospective study raises the therapeutic dilemma of what constitutes optimal treatment for this tumor.

The case of neurocytoma reported here demonstrates rare mitoses and necroses without evidence of vascular proliferation. We elected to limit treatment to surgical resection without postoperative radiation. Clinically he remains symptom-free, and annual CT scans show no evidence of recurrence after 24 months following surgical intervention. The paucity of cases reported to date are insufficient to determine the propensity for recurrence. Our case is the seventh reported case of neurocytoma showing mild anaplastic changes. Continued long-term observation of these cases will help provide further information on the recurrent nature of neurocytomas and the necessity for use of radiation in the treatment of this newly classified tumor.

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Neurocysticercosis:

Report of Fifteen Cases

MARTHA BUITRAGO, M.D., BARBARA EDWARDS, M.D., AND FRED ROSNER, M.D.

Abstract

Background: Neurocysticercosis (NCC), which is caused by the encysted larvae of the porcine tapeworm *Taenia solium*, is uncommon in developed countries.

Methods: Fifteen cases were reviewed retrospectively from the medical records of patients admitted to Queens Hospital Center, a 550-bed acute care municipal hospital in New York City, from 1986 through 1992. All patients were immigrants from Central and South America. Nine were men and six were women; age range was 11–80 years, mean 33.8 years. Thirteen of the 15 patients (86%) were admitted with seizures. One patient had a strokelike syndrome with transient slurred speech and confusion.

Results: Diagnosis was based on clinical findings, CT or MRI studies (100%), and ELISA titers (81%). Cerebrospinal fluid abnormalities were noted in 5 of 7 samples obtained. Twelve adult patients with NCC were treated with praziquantel and steroids, and their courses were uncomplicated, except for one patient who required ventricular shunt placement for hydrocephalus.

Conclusions: NCC should be suspected in immigrants from Central and South America who have seizures; it may complicate the differential diagnosis of various central nervous system syndromes. Available therapies entail risks and uncertainties. The ultimate approach is prevention of infestation.

NEUROCYSTICERCOSIS (NCC), the central nervous system infection caused by *Taenia solium*, is a rare disease in developed countries. It is a treatable cause of seizure disorder and should be considered in the differential diagnosis. We present fifteen cases of NCC diagnosed and treated at a municipal hospital in the city of New York.

Materials and Methods

A search was conducted of the files of the Infectious Diseases Division of the Department of Medicine, the Neurology Department files, and the Queens Hospital Center medical records de-

partment to identify cases of neurocysticercosis in patients seen at the hospital from 1986 to 1992. Also reviewed were the records of the serology laboratory to identify patients from whom cysticercosis antibody titers were ordered during that time period.

Using hospital record numbers thus identified, individual charts were reviewed and the following data extracted: admission date, sex, age, race, country of origin, hospital site of presentation, initial signs and symptoms, neurologic findings, serum and spinal fluid cysticercosis titers, cerebrospinal fluid findings, and results of computerized tomography (CT) scans, magnetic resonance imaging (MRI), electroencephalograms (EEGs), eye examination, and soft-tissue radiographs. Treatment, outcome, and followup were also recorded for each patient.

Neurocysticercosis was diagnosed if a patient gave an appropriate medical history and had neurologic and radiologic findings typical or highly

From the Departments of Medicine at Mount Sinai Services at Queens Hospital Center, Jamaica, NY, and at Mount Sinai School of Medicine, New York, NY. Address correspondence and reprint requests to Fred Rosner, M.D., Director, Department of Medicine, Queens Hospital Center, 82-68 164th Street, Jamaica, NY 11432.

suggestive of NCC. Cerebrospinal fluid (CSF) cysticercosis titers or serum serologic analyses were obtained for most of the 15 patients.

Results

Fifteen charts were available for review of patients diagnosed as having NCC between 1986 and 1992. There were nine men and six women (Table 1). They ranged in age from 11 to 80 years at the time of diagnosis. Of the 15 patients, 5 were from Haiti, 4 from El Salvador, 2 from Mexico, and 1 each from Honduras, Guatemala, and Ecuador. One patient was Hispanic but his country of origin was not stated.

Diagnosis. Initial clinical features varied. Thirteen patients had seizures; 10 of them had generalized seizures and 3 had partial seizures. Two of these 3 had secondarily generalized seizures. Three patients had severe headache; 1 of these had signs of increased intracranial pressure. Other initial features were: a strokelike syndrome with transient slurred speech and confusion (pt 12), productive cough and fever (pt 3, who had pulmonary tuberculosis associated with NCC); blurred vision and lethargy (pt 8).

The initial neurologic examination suggested a focal or mass lesion in several patients. There were cranial nerve palsies in 2 patients. One patient each had hemianesthesia, weakness, and

meningeal signs. However, 12 patients had normal results on initial neurological examination.

Electroencephalography in 9 patients showed slowing with diffuse cerebral dysfunction in 3, abnormal sharp waves in 1, and a focal abnormality compatible with a focal structural lesion in 1. Four patients had normal results on EEG.

Computed tomographic scans suggested active disease demonstrated by mass lesions in 12 patients. Ten of these patients had parenchymal disease, and 5 of these showed a mass effect secondary to cysts (Fig. 1). Two patients had subarachnoid cysts. Calcifications representing inactive disease were noted in 2 patients. Of the 6 patients who had soft-tissue radiographs performed, 4 had skeletal muscle calcifications compatible with cysticercosis (Fig. 2). No evidence of ocular cysts was found in any of the 10 patients who had ophthalmologic examinations.

Taenia sp. eggs were found in stool samples from one of six patients tested. Other parasites found included *Endolimax nana* and *Blastocystis hominis*, hookworm, *Ascaris lumbricoides*, and the head of *Taenia spp.*

The CSF was examined in eleven patients (Table 2). Pleocytosis (WBC > 10/cc) was found in 5 patients. The cells were mostly monocytes. Elevated protein and eosinophils were found in only 1 patient.

TABLE 1
Demographic Data and Clinical Characteristics of 15 Patients with Neurocysticercosis

Pt. no.	Age (yrs)	Sex	Country of origin	Site of hosp. presentation	Underlying illness	Initial symptoms	Results of neurologic exam
1	30	M	Haiti	Clinic	Sickle cell disease	Headache	Normal
2	26	F	Honduras	ER	None	Headache, fever	Normal
3	22	M	Haiti	ER	Pulmonary TB	SZ, cough, fever	Normal
4	11	F	Haiti	ER	None	SZ	Normal
5	44	M	Unknown*	ER	None	SZ, headache	Photophobia, weakness left arm
6	36	F	El Salvador	Clinic	None	SZ, dysphagia	Normal
7	14	M	Haiti	Clinic	None	SZ	Normal
8	26	M	Mexico	ER	None	SZ, blurred vision	Bilateral abducens palsy
9	80	F	Guatemala	ER	None	Focal SZ, LOC	Normal
10	23	M	Mexico	ER	None	SZ	VII nerve palsy, left hemianesthesia, behavioral changes
11	56	M	Haiti	Clinic	None	SZ	Normal
12	69	F	El Salvador	PMD	None	SZ, slurred speech	Normal
13	30	F	El Salvador	ER	None	SZ	Normal
14	27	M	Ecuador	ER	None	SZ	Normal
15	14	M	El Salvador	ER	None	Focal SZ	Normal

M, male; F, female; ER, emergency room; PMD, private medical doctor; SZ, seizure; LOC, loss of consciousness.

* Patient was Hispanic.

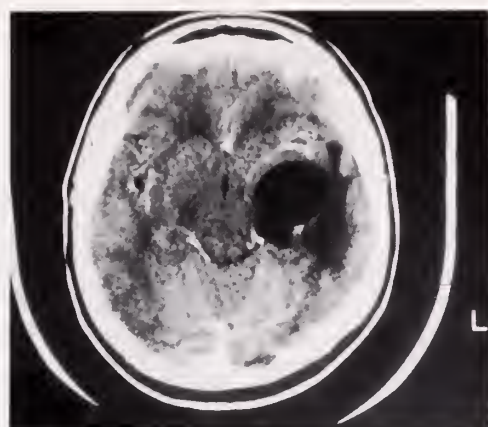


Fig. 1. Subarachnoid cyst in a patient with neurocysticercosis.

The ELISA results were positive in serum or CSF or both in 12 of 13 patients (92%).

Treatment. Praziquantel combined with steroids was used for treatment in 11 patients. One patient received praziquantel without steroids. Three patients were treated with anticonvulsants only. One patient required readmission to the hospital; this patient had a shunt placed for ventricular obstruction, and subsequently had recurrent episodes of shunt malfunction and infection.

Follow-up radiological studies (CT/MRI) were performed in 12 patients (Table 3). Resolution of the disease, smaller cysts, or ring enhancement was documented in 8 patients. One patient, noncompliant in taking medication, had multiple new lesions in a follow-up CT scan. Three others had no significant changes on CT scan.



Fig. 2. Calcifications in skeletal muscle in a patient with neurocysticercosis.

During followup, the most common complaints were mild headache (3 patients) and persistence of blurred vision and numbness (1 patient). Seven patients were free of seizures and asymptomatic during the follow-up period (Table 4).

Discussion

Neurocysticercosis (NCC) is an infection of the central nervous system (CNS) caused by the larval form of *Taenia solium*, the porcine tapeworm, for which the human being is the only definite host (1–2). The parasite is acquired by humans ingesting undercooked infected pork or by

TABLE 2
Serum Cysticercosis Titers and Cerebrospinal Fluid Findings in 15 Patients with Neurocysticercosis

Pt. no.	Serum titer	CSF titer	Cerebrospinal fluid findings						
			RBC/dl	WBC/dl	Monos (no.)	Polys (no.)	Eos (no.)	Protein (mg)	Glucose (mg)
1	1/320	1/32	1730	136	127	0	9	44	49
2	1/2056	Not done	20	1015	88	12	0	90	51
3	Not done	1/8	0	1	1	0	0	10	70
4	1/80	1/8	0	107	97	10	0	34	72
5	1/640	Not done	7	1	0	1	0	31	61
6	1/320	<1/2	145	0	0	0	0	24	55
7	Negative	Not done	640	8	6	2	0	25	51
8	Not done	Not done	Not done	Not done	Not done	Not done	Not done	Not done	Not done
9	Not done	1/320	70	147	74	73	0	227	45
10	Not done	Not done	0	0	0	0	0	27	78
11	1/320	Not done	Not done	Not done	Not done	Not done	Not done	Not done	Not done
12	1/640	Not done	Not done	Not done	Not done	Not done	Not done	Not done	Not done
13	1/160	Not done	Not done	Not done	Not done	Not done	Not done	Not done	Not done
14	1/32	1/32	1	12	10	2	0	25	103
15	1/20	1/20	0	0	0	0	0	16	78

CSF, cerebrospinal fluid; RBC, red blood cells; WBC, white blood cells; Monos, monocytes; Polys, neutrophils; Eos, eosinophils.

TABLE 3
Laboratory Studies in 15 Patients with Neurocysticercosis

Pt. no.	First CT scan			Second CT scan	EEG	Eye exam	Soft-tissue x-ray
	Site	No. of cysts	No. of calcific.				
1	Parenchymal	Single	Multiple	Ring enhancement	Not done	Not done	Normal
2	Parenchymal	Single	None	No change	Not done	Normal	Not done
3	Parenchymal	Multiple	Multiple	Smaller lesions	Diffuse dysfunction	Not done	Not done
4	Parenchymal	Single	Multiple	Not done	Not done	Not done	Not done
5	Parenchymal	Single	Multiple	Ring enhancement	Focal dysfunction	Normal	Normal
6	Parenchymal	None	Single	MRI normal	Not done	Normal	Not done
7	Parenchymal	None	Multiple	Multiple calcifications	Normal	Normal	Not done
8	Subarachnoid	Single	Multiple	Not done	Diffuse slowing	Not done	Not done
9	Subarachnoid	Multiple	Multiple	Many new lesions	Generalized slowing	Normal	Calcifications
10	Parenchymal	Single	None	Not done	Not done	Normal	Not done
11	Parenchymal	Single	Multiple	Mild hydrocephalus	Normal	Normal	Not done
12	Parenchymal	Multiple	None	Ring enhancement	Abnormal sharp waves	Normal	Calcifications
13	Parenchymal	Multiple	None	No change	Not done	Normal	Calcifications
14	Parenchymal	Single	Multiple	New subarachnoid cyst	Normal	Not done	Normal
15	Parenchymal	Single	None	Smaller cyst	Normal	Normal	Not done

accidental ingestion of tapeworm eggs in contaminated food or water (1). Rarely, autoinoculation can occur when eggs are ingested by the fecal-oral route.

Once ingested, the eggs lose their coat in the human digestive tract and liberate oncospheres (hexacant embryos) that, in turn, cross the intestinal wall, enter the blood stream and lymphatics, and are carried to the host's skeletal muscles, eye, subcutaneous tissue, heart, and brain. After a period of two months, the larvae evolve into cysticerci (1-3).

The disease is particularly common in Mexico, other parts of Central and South America, Africa, India, Eastern Europe, and Indonesia (4-6). Because of immigration from these areas, NCC is being diagnosed with increasing frequency in developed countries (3, 7-12). Large series were reported in Europe following the return of World War II service personnel from endemic areas such as India (2, 13), but public health strategies have since reduced the prevalence (7).

Natural History. The natural history of the CNS infection has been well documented, both histologically and radiologically (14-16). The clinical course of the disease depends on the patient's immune response, the severity of the infestation, and the location and number of NCC lesions (3, 5). Over the past decade, radiologic imaging of the brain using CT scan and magnetic resonance imaging have become the most important tools in diagnosing NCC and assessing the activity and severity of the disease (1-4, 14-16).

Healthy, living cysticerci are essentially inert and cause minimal tissue damage and inflammation (17). CT scanning can demonstrate non-

enhancing cystic lesions without edema, due to absence of an inflammatory response around the cyst. This stage of infection is clinically asymptomatic unless the anatomic site of cysts causes pressure on or obstruction of vital CNS structures. This stage is known as the vesicular stage on pathological examination (14-17). A cysticercus may live 18 months to 10 years (17).

As the parasite begins to degenerate, capsular integrity is lost. Acute encephalitis ensues from humoral and tissue responses to the cysticerci. This stage is characterized by ring-enhancing lesions with surrounding edema. Occasionally, the cyst wall calcifies, an eccentric dot of calcium representing the protoscolex of the parasite. On pathologic examination this stage is called the colloid vesicular stage. When a cyst retracts, its contents mineralize, and the capsule thickens and involutes. Granulomatous lesions result and appear as enhancing nodules or microrring-like lesions with or without surrounding edema. This is the granular nodular pathologic stage. The majority of patients become symptomatic at this time (14-17). Once the cyst has shrunk and completely mineralized, the nodules appear calcified and hypointense and fail to enhance after administration of contrast material. This is the nodular calcified stage. Contrast enhancement occurs when there are both surrounding edema and probable degeneration of the worm and inflammatory reaction of the adjacent brain tissue (14-16).

Diagnosis and Treatment. Electroencephalograms, radiographs of soft tissue, and serological tests for cysticercosis give additional information but may not be diagnostic of NCC (17-20). In the

TABLE 4
Treatment and Outcome in 15 Patients with Neurocysticercosis

Pt. no.	Treatment	Outcome	Follow-up
1	Praziquantel-prednisone	Improved	No complaints
2	Praziquantel-prednisone	Improved	Asymptomatic
3	Praziquantel-prednisone-phenytoin	Improved	Seizure-free
4	Phenytoin	Improved	None
5	Praziquantel-decadron-phenytoin	Improved	None
6	Praziquantel-prednisone-phenytoin	Improved	Seizure-free
7	Carbamazepine-phenytoin	Improved	None
8	VP shunt-praziquantel-prednisone	No change	None
9	Praziquantel-prednisone-phenytoin	No change	Tingling left leg, blurred vision
10	Praziquantel-prednisone	Improved	None
11	Praziquantel-phenytoin	Improved	Mild headache, seizure
12	Praziquantel-prednisone	Improved	No complaints
13	Praziquantel-prednisone	Improved	Mild headache, seizure-free
14	Praziquantel-prednisone-phenytoin	Improved	Seizure-free
15	Phenytoin-carbamazepine	Improved	Seizure-free

CNS, cysticerci can lodge in the brain parenchyma. Usually this produces seizures in the patient. Seizures affected 84.6% of our patients with parenchymal disease. If the parasite is in the subarachnoid space, signs of increased intracranial pressure with secondary hydrocephalus may develop. If the intraventricular system is infected with cysticerci, the patient may have severe headache or vomiting. The patient in this series who had intraventricular and subarachnoid cysts had syncope, focal neurologic signs, and behavioral changes. Spinal infestation, either leptomeningeal or intramedullary, may also occur (1, 2, 5, 11).

A particularly severe and aggressive form of NCC is a racemose meningobasal form, in which a group of cysts arborize into extensive grapelike clusters around basal cisterns, resulting in hydrocephalus and dementia (1, 3). Other active forms of the disease include arachnoiditis with increased mononuclear cells and protein and a positive immunologic test for cysticercosis in the CSF or hydrocephalus secondary to meningeal inflammation, parenchymal cysts, and spinal cysts (3). Inactive forms of NCC can occur with parenchymal calcifications and hydrocephalus secondary to meningeal fibrosis (3, 17).

The combination of clinical and radiologic findings in each individual provides the outline for the difficult process of diagnosis and treatment. Serologic tests that reveal antibodies to *Taenia solium* can support a clinical diagnosis. Anticysticercal drugs are effective against living (active) cysts (3, 20). Praziquantel has been shown to be effective in numerous series of patients (21–23). Some authors recommend the addition of steroids to reduce the cerebrospinal fluid reaction syndrome, described as intracranial hypertension

secondary to edema around the dying parasites (23).

Recent studies (24–27) suggest that albendazole may be significantly more effective than praziquantel in reducing the total number of cysts as shown by CT scans (28). However, albendazole therapy results in a higher frequency of neurologic sequelae (28). Albendazole is not available in the United States.

Praziquantel therapy is generally well tolerated. Some trials have reported mild and transient symptomatic side effects, such as abdominal discomfort, nausea, vomiting, anorexia, diarrhea, headache, vertigo, and dizziness. Of the 12 patients treated with praziquantel, 10 completed the treatment (83%). Two patients complained of mild headache secondary to the medication. Since these effects are transient, compliance with medication intake has been good. The high cost of the drug limits its use in developing countries (29). Long-term albendazole treatment is associated with an increase in levels of transaminases, neutropenia, and alopecia (30).

For inactive forms of NCC, therapy should be directed to the control of clinical sequelae of NCC such as epilepsy and hydrocephalus.

Surgical management should be directed to large cisternal and parenchymal cysticercal cysts if they are rapidly progressive or refractory to medical therapy (31).

Clinical Outcomes. The clinical outcome in our patients was favorable. The majority (87%) had clinical and radiologic improvement with medical therapy. A poor outcome occurred in the patient with intraventricular cysts resulting in hydrocephalus. Intraventricular shunt was performed, which resulted in shunt obstruction and infection.

Considering the risks and fallibility of anticysticercal therapy, the ultimate approach to this disease continues to be prevention of infestation by improving water supplies, adequately cooking pork, and improving personal hygiene (7, 28).

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Cough Induced by Angiotensin-Converting-Enzyme Inhibitors:

Airway Responses to Inhalation of Methacholine in Patients Who Have Essential Hypertension

JAMES P. KELLEHER, M.D., FERNANDO ELIJOVICH, M.D., CHERYL L. LAFFER, M.D., PH.D., AND MARIA PADILLA, M.D.

Abstract

We investigated whether patients with cough due to angiotensin-converting-enzyme inhibitors have a common pattern of airway responses to methacholine inhalation. Studies assessing only presence or absence of hyperresponsiveness to this agent have produced conflicting results. Spirometric testing before and after methacholine was performed in 14 hypertensive patients at least two weeks after discontinuation of these inhibitors, when cough had abated or disappeared. Subjects were predominantly female (86%) nonsmokers (93%), with high prevalence of respiratory atopic illnesses (57%) probably due to ethnic background (72% Hispanic). Premethacholine spirometric values were normal. Postmethacholine bronchoconstriction of varying degrees was observed in seven patients, but reached the level of hyperresponsiveness in only one patient with asthma. The other seven subjects exhibited no bronchoconstriction. The two groups did not differ in age, concomitant illnesses (e.g., atopy) and medications, or blood pressure reduction. We conclude that airway responses to cholinergic stimulation do not exhibit a common pattern and are randomly distributed in hypertensive patients who develop cough induced by angiotensin-converting-enzyme inhibitors.

DRY COUGH is a relatively common side effect of the angiotensin-converting-enzyme inhibitors (ACEIs) (1) and is observed in patients who use these agents for the treatment of hypertension (2) or congestive heart failure (3). Cough represented up to 39% of the side effects reported as produced by these agents in one series (4). Its overall incidence may be as high as 31% (2), depending on whether the symptom is voluntarily mentioned by the patient or the physician directly asks the patient if the symptom has occurred (1). It is

somewhat puzzling that the mechanism of this common side effect is not yet clearly understood.

Several hypotheses for the mechanism of this cough have been proposed, including a direct effect of these inhibitors on prostaglandin synthesis (5) or on substance P (6), as well as indirect effects mediated by diminished degradation of bradykinin (7–10). If any of these mechanisms were solely responsible, cough would be present in all users of these agents. It has therefore been speculated that this cough may require an underlying abnormality in airway responsiveness or cough threshold. These issues have been explored by assessing the bronchoconstrictor effects of histamine (11) or methacholine (2, 12–14) and the cough reflex response to capsaicin (15–17) or citric acid (11, 18). Results have been conflicting (11–14, 16).

From the Department of Medicine, Mount Sinai School of Medicine, New York, NY. Address reprint requests to Fernando Elijovich, M.D., Associate Professor of Medicine, University of Texas Medical Branch at Galveston, 4.156 John Sealy Hospital, Route 0572, Galveston, TX 77555-0572.

TABLE 1
Demographic and Clinical Characteristics, 14 Patients

Pt	Age	Race	Sex	Hx	
				Smoking	Atopy
1	66	Hisp	F	past	
2	66	Hisp	F	never	
3	72	Hisp	F	never	
4	69	Hisp	F	never	Asth
5	62	Wh	F	never	
6	67	Hisp	M	past	Rhin
7	58	Bl	F	never	
8	69	Hisp	F	now	Asth
9	56	Hisp	F	past	Fam
10	75	Bl	F	never	
11	73	Hisp	F	never	Fam
12	73	Hisp	F	never	Rhin
13	77	Wh	F	never	Rhin
14	58	Hisp	M	never	Rhin

Bl, African-American; Hisp, Hispanic; Wh, white; Asth, asthma; Rhin, allergic rhinitis; Fam, family history of asthma or allergic rhinitis.

Among the advantages of the methacholine challenge as a test of bronchial responsiveness are that it is well standardized (19) and that it explores the effects of physiologic parasympathetic stimulation. However, responses to methacholine may be exaggerated in many respiratory disorders, such as asthma (20, 21), allergic rhinitis (20–22), chronic bronchitis (23), sarcoidosis (24), and cystic fibrosis (25), and in nonrespiratory disorders such as left ventricular dysfunction (26) and could theoretically be modified by commonly used medications, such as the nonsteroidal antiinflammatory drugs (16, 27) and the α 1 blockers (28), the beta blockers (18), and the calcium channel blockers (29).

We carried out methacholine challenge tests after discontinuation of ACEIs in 14 patients who had essential hypertension and developed cough during treatment with these agents. We set out to explore whether a consistent pattern of airway responses suggested a common disorder underlying these patients' cough, or whether, in contrast, varied responses to methacholine could be related to concomitant illnesses or therapies.

Methods

This study was designed as a case series and was carried out at the medical clinic of the Department of Medicine. Two of the authors (CL, FE) evaluated all patients (known or referred to them) who complained of a cough while taking ACEIs. One of the patients was a participant in an IRB-approved drug efficacy trial of the non-marketed ACEI zofenopril. Although the study

was advertised among faculty, trainees, and nurses to increase recruitment, no systematic attempt was made to guarantee that all potential candidates were identified. Therefore, this study cannot draw conclusions about the prevalence of ACEI-induced cough in our clinic population.

Patients were considered to have ACEI-induced cough if this symptom (a) definitely began after initiation of ACEIs, as shown in review of history, (b) was described as dry, nonproductive, or coming from an "itchy" or "scratchy" throat, (c) had no other apparent cause by history, physical examination, or additional study such as chest x-ray, and (d) improved or disappeared soon after discontinuing the ACEI. The investigators agreed on seeking out the information on each of these four criteria systematically in all patients referred to them for evaluation of possible ACEI-induced cough. However, no specific instrument such as a questionnaire was used for this purpose. A formal rechallenge with ACEIs was not carried out in any of our subjects.

Fifteen patients were identified over two and a half years. The investigators obtained a careful history, conducted a physical examination, and performed routine blood tests to exclude alternative diagnostic explanations for the cough and to assess concomitant illnesses and therapies. ACEIs were discontinued after the investigators concluded that these agents were probably responsible for the cough, whatever the previous blood pressure response to these agents (responders defined as having sustained a decrease of ≥ 15 mm Hg systolic or ≥ 5 mm Hg diastolic). Antihypertensives belonging to other drug families were substituted as needed. Pulmonary function tests (PFTs) with a methacholine challenge were scheduled for at least two weeks after discontinuation of ACEIs. All fifteen patients underwent this evaluation. However, only fourteen studies are reported because PFT results were deemed to be inaccurate in one patient, due to poor effort.

PFTs were conducted at the laboratory of the Pulmonary Division of the Department of Medicine using standard techniques. In brief, patients arrived at the laboratory and, after resting for approximately 15 minutes, were given a demonstration of appropriate spirometric techniques with a Med Graphic 1070 apparatus. Study measurements were not carried out until these preliminary curves were deemed acceptable (expiratory flow for a minimum of 6 seconds and continued effort despite cessation of flow for at least 2 additional seconds). Baseline spirometric values were measured after inhalation of five breaths of the methacholine diluent. Postmeth-

acholine curves were obtained 3–5 minutes after the fifth breath of methacholine solutions at 5 and 10 mg/mL (all patients) and 25 mg/mL (three patients). All results are reported for the best effort of three consecutive curves differing by less than 10%. Baseline spirometric values are reported in absolute values and also as a percentage of predicted values, following Miller et al. (30). Each result after the maximum dose of methacholine is reported as a percentage of the premethacholine value. When the term "bronchial hyperresponsiveness" (a positive methacholine challenge) is used, it refers to a postmethacholine FEV1 $\leq$ 80% of the premethacholine value—a reduction of $\geq$ 20% from baseline—following Chai et al. (19).

Data are presented as mean $\pm$ SEM. Student's paired and unpaired *t*-tests and Wilcoxon's rank sum test were carried out with the SAS package (SAS Institute, Cary, NC) available at the mainframe computer of the City University of New York. A probability value of less than 5% was used to reject the null hypothesis.

Results

Demographically (Table 1), most of the subjects were middle-aged (67 ± 1.8 yrs) Hispanic (72%) women (86%), consistent with the prevalence of these characteristics in our clinic population. Only one of the patients was a current smoker; ten of them (71%) had never smoked. More than half of the patients (57%) had a personal or family history of asthma or allergic rhinitis.

None of the patients had serum creatinines over 1.5 mg/dL and only one had proteinuria. Nine subjects had EKG abnormalities (hypertensive left ventricular hypertrophy, *n* 4, ischemic heart disease, *n* 3, or both, *n* 2) but only two had clinically significant heart disease (angina with preserved systolic left ventricular function in one and history of myocardial infarction with systolic left ventricular dysfunction in the other). Two additional patients, both older than 70, had echocardiographic evidence for diastolic left ventricular dysfunction, without concomitant clinical or electrocardiographic abnormalities.

The four converting enzyme inhibitors were given in conventional dosages (Table 2). Cough developed within three months (57.1%) to one year (71.4%) in most patients, but onset took longer than five years in one. Although data suggest that the interval to onset of cough was longer for enalapril than for the other agents, statistical analysis (Wilcoxon rank sum test) did not reveal any significant difference.

TABLE 2
Time Relationships between Angiotensin-Converting-Enzyme Inhibitors (ACEI), Cough, and Pulmonary Function Tests (PFTs)

Pt	Drug	Dose (mg/day)	Interval		
			ACEI—cough (days)	End ACEI—end cough (days)	End ACEI—PFTs (days)
1	E	5–10	27	75	71
2	E	5–10	239	1	192
3	C	75	1	23	35
4	E	20	1924	26	33
5	E	5–10	31	5	19
6	E	10	553	37	34
7	C	50	217	112	66
8	E	10	81	92	17
9	E	10	392	49	29
10	C	50	9	63	28
11	E	10	451	7	23
12	Z	60	52	35	22
13	E	5	61	63	28
14	L	10	28	22	18

C, captopril; E, enalapril; L, lisinopril; Z, zofenopril.

TABLE 3
Baseline Pulmonary Function Tests, 14 Patients

Function	Mean $\pm$ SEM	(Range)
FVC (L)	2.55 $\pm$ 0.17	(1.45–3.50)
FVC (% predicted)	94.7 $\pm$ 5.0	(70.0–133.0)
FEV1 (L)	2.04 $\pm$ 0.13	(1.32–3.01)
FEV1 (% predicted)	97.0 $\pm$ 4.5	(78.0–135.0)
FEV1/FVC	80.50 $\pm$ 1.70	(70.00–91.00)
FEV1/FVC (% predicted)	103.2 $\pm$ 2.2	(91.2–117.9)
FEF25–75 (L/sec)	2.13 $\pm$ 0.26	(1.01–4.47)
FEF25–75 (% predicted)	100.5 $\pm$ 11.8	(51.0–194.0)
FEF MAX (L/sec)	5.52 $\pm$ 0.53	(3.40–9.24)
FEF MAX (% predicted)	109.4 $\pm$ 7.8	(70.0–161.0)
MET (sec)	0.68 $\pm$ 0.08	(0.30–1.30)

FVC, forced vital capacity; FEV1, expiratory volume of the 1st second; FEF25–75, midexpiratory flow; FEF MAX, peak expiratory flow; MET, mean expiratory time.

Disappearance of cough was noted by eight patients within the first six weeks after discontinuation of therapy, and in all but one patient within three months. The minimum interval between discontinuation of the ACEI and the measurements of pulmonary function was 17 days. In most patients (79%), these tests were carried out after patients had discontinued therapy for three to five weeks. In some patients, cough had not completely abated at the time of testing.

The aggregate baseline spirometric measurements were normal in this group of patients; average FVC, expiratory volumes, and flows were essentially not different from predicted values (Table 3). Analysis of individual data disclosed no

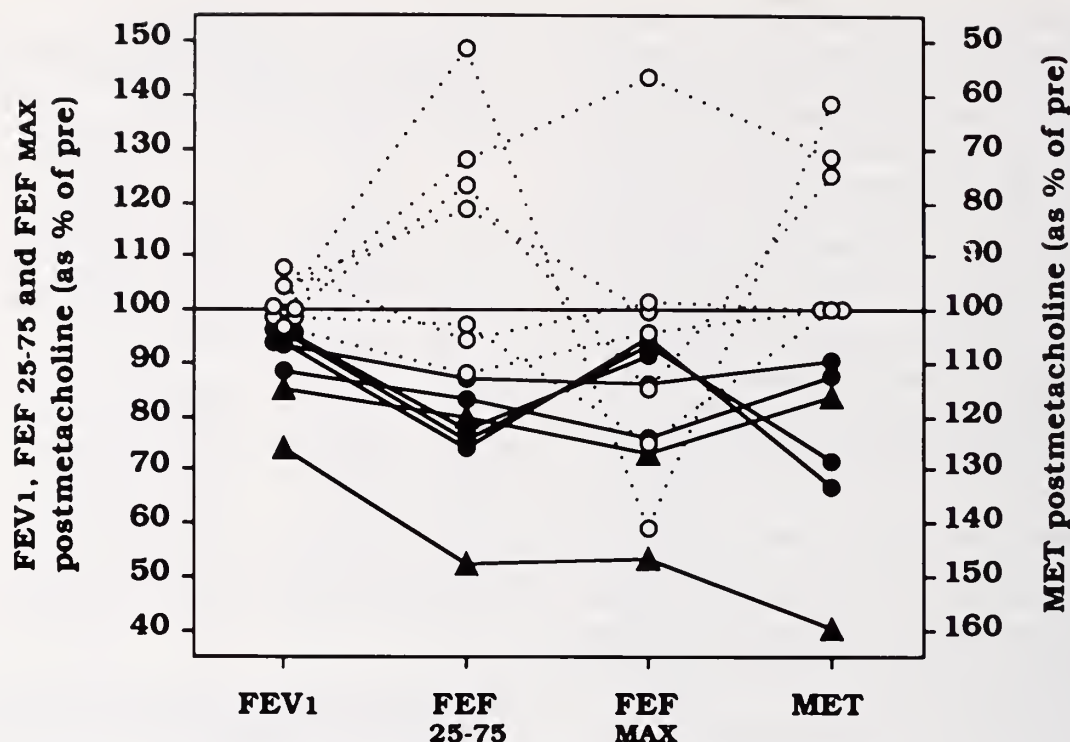


Fig. Spirometric values after methacholine as percentage of premethacholine values. FEV1, forced expiratory volume in one second; FEF25-75, maximum expiratory flow rate during middle half of expiration; FEF MAX, peak expiratory flow rate; MET, mean expiratory time. Individual values for four parameters in each subject are joined by lines. Black triangles, data on two patients with asthma. Black circles, data on five patients all of whose postmethacholine tests indicated some degree of bronchoconstriction. White circles, data on remaining seven patients. Black and white symbols differentiate two subgroups.

abnormalities in the two asthmatic patients (one of whom was a current smoker), obstructive involvement of the small airways (FEF25-75 below the lower 95% confidence limit) in two of the four patients with allergic rhinitis, and a mild reduction of FEV1/FVC in a patient without a clear history of respiratory ailments or smoking.

The results of spirometric measurements after methacholine administration reveal two subgroups, represented by black and white symbols in the figure. The two asthmatic patients (black triangles) sustained the largest reductions in FEV1, 15% and 26.5%. The latter patient, therefore, was the only one of the group who exhibited bronchial hyperresponsiveness to methacholine. Methacholine-induced bronchoconstriction of varying degrees was observed in 5 of the 12 nonasthmatic patients (black circles). In these patients, methacholine reduced FEV1 by 4%–12% and produced consistent reductions in mid and peak expiratory flows (6%–26%) and prolonged expiratory times (10%–33%). In contrast, spirometric measurements after methacholine in the remaining 7 patients (white circles) exhibited a random pattern; individual and group FEV1s, ex-

piratory flows, and expiratory times were widely scattered above and below baseline values.

Neither the method of testing nor patients' clinical characteristics explained the apparent difference in methacholine responses between these two subgroups. The characteristics of methacholine responders vs nonresponders were as follows: (a) mean maximal dose of methacholine used, 14.2 ± 2.7 (n = 7) vs 12.2 ± 2.2 mg/mL (n = 7), ns; (b) number of patients with asthma, allergic rhinitis, or a family history of either, 4/7 vs 4/7; (c) presence of systolic or diastolic left ventricular dysfunction, 1/7 vs 2/7; (d) use of nonsteroidal antiinflammatory drugs, 3/7 vs 1/7; (e) use of calcium channel blockers, 2/7 vs 1/7; and (f) mean age, 68 ± 2 vs 66 ± 3 years, $p = 0.6$.

In addition, the mean methacholine-induced change in FEV1 in patients with a personal or family history of allergic disorders, $-1.7 \pm 1.6\%$, did not differ from that in patients without such history, $-3.1 \pm 2.6\%$, $p = 0.67$. Finally, blood pressure responders ($169 \pm 7/91 \pm 4$ to $142 \pm 6/82 \pm 3$, $\Delta = -26 \pm 6/-9 \pm 3$ mmHg, n = 7, $p < 0.003/p < 0.03$) and nonresponders to ACEIs ($145 \pm 4/87 \pm 4$ to $145 \pm 2/88 \pm 4$, $\Delta = 0 \pm 6/1 \pm 2$

mmHg, $n = 7$, ns/ns) did not differ in mean methacholine-induced change in FEV1. The value of Δ FEV1% was, respectively, $-3.7 \pm 2.9\%$ and $-6.4 \pm 3.7\%$, $p = 0.57$.

Discussion

Previous studies investigating the possibility that ACEI-induced cough occurs only in patients with airway hyperreactivity have produced conflicting results (2, 11–14). In studies using a methacholine bronchoconstrictor challenge, patients were labeled as having “positive” or “negative” responses. This dichotomous classification employs cutoffs derived from asthmatic patients, who have classic airway hyperreactivity. The most commonly used cutoffs are a methacholine-induced reduction in FEV1 of $\geq 20\%$ (19) or a methacholine-PC20 (the concentration producing such reduction) of < 8 mg/mL (31). Whether a common pattern of methacholine response not reaching the magnitude of a “positive” methacholine challenge test is present in patients with ACEI-induced cough has not been reported. We studied the effect of inhaled methacholine on several respiratory function parameters (FEV1, mid-expiratory flows, and expiratory times) in a group of essential hypertensives with ACEI-induced cough, after patients had discontinued taking these agents. Some of the patients had hypertensive complications (26) and concomitant illnesses (20–22) or received therapeutic agents (16, 29, 32, 33) known to affect airway reactivity. We assessed the effect of these possible confounders on our results.

We found 15 patients with ACEI-induced cough over 2.5 years in a clinic caring for approximately 6,000 subjects, 45% of whom have essential hypertension. We did not attempt to identify all cases (see Methods). Also, the study was conducted when this symptom was not yet a well-recognized side effect of ACEIs, so that physicians and trainees may not have been aware of it. Therefore, these observations do not represent an estimate of the prevalence of this side effect in the clinic population we studied. The patient receiving zofenopril was one of 16 participants in an efficacy trial of this nonmarketed ACEI. Therefore, in this trial, prevalence was 6.2%, a figure in the middle of the reported range (2, 34) for ACEI-induced cough.

Diagnosis of ACEI-induced cough was not established by means of a formal rechallenge. However, alternative causes were thoroughly excluded, and the characteristics of the cough (dry,

nonproductive, with a “scratchy” throat) were consistent with observations by others (34–36). The greater representation of women among patients with ACEI-induced cough (1, 4, 14, 34, 35) may be due to greater sensitivity to cough-inducing maneuvers in normal women (37). However, we cannot exclude the possibility that the gender distribution of our patients merely reflects that of our clinic population. Analogously, although some have reported that ACEI-induced cough is more common in nonsmokers (14, 36, 38), the low prevalence of smokers in our series may reflect low smoking rates in Hispanic women (39).

Only one patient exceeded the two-year maximum reported interval from the beginning of ACEI therapy to the onset of cough (13). This subject had been taking an enalapril tablet provided by the manufacturer (compassionate basis) for five years but did not develop cough until 4 months after being switched to a commercially available preparation. We did not find other reported cases suggesting that the cough could be due to the vehicle rather than to the ACEI. The interval to onset of cough was somewhat longer for enalapril than for the other agents. However, the difference was not statistically significant, and the observation is the opposite of results in another group (34). Reported intervals from discontinuation of ACEIs to cessation of cough have varied from a few days (35) to four weeks (40). In half of our patients, however, a very mild cough persisted for a somewhat more prolonged period, not exceeding 16 weeks.

More than half of our patients had either a personal or a family history of an atopic respiratory disorder. This was present in 70% of the Hispanics while in only 25% of Caucasians and African-Americans combined. Whether this finding reflects an ethnic genetic predisposition, as previously reported in Puerto Ricans in New York City (41), or is due to environmental or other factors cannot be ascertained from our study. If ACEIs had specific effects on PFTs of patients with respiratory atopy, our results could have been confounded by those effects. However, it has been shown that ACEIs do not modify pulmonary function of normotensive (42) or hypertensive asthmatics (12, 43, 44), even when circulating levels of ACE are markedly inhibited (42).

Four of our patients were taking aspirin or cyclooxygenase inhibitors (NSAIDs) for the management of pain. These agents should suppress ACEI-induced cough if prostaglandins were mediators of this symptom. Prostaglandins E2 (45), F2 α (45), and thromboxane A2 (9) respectively

stimulate C fibers, activate "irritant" receptors, and directly constrict the airway. Their synthesis is increased by the sulfhydryl group of some ACEIs (5) or by bradykinin, the degradation of which is reduced by ACEIs (8). Moreover, PGE₂ specifically increases cough responses to capsaicin in normal volunteers (27). Initial studies with the NSAID sulindac suggested that this agent abolished ACEI-induced cough (33) and that its antitussive effect (associated with attenuation of the capsaicin-induced cough reflex) was specific, that is, not observed in other forms of nonproductive dry cough (16). However, a recent double-blind study (46) has failed to confirm that sulindac suppresses ACEI-induced cough. This is consistent with our finding of cough developing in patients taking cyclooxygenase inhibitors. Similar to our observations with NSAIDs, two of our patients developed cough despite use of theophylline, an agent reported to alleviate ACEI-induced cough in a manner unrelated to bronchodilation (32).

Despite the high prevalence of respiratory atopy, PFTs were well preserved in this group of patients as a whole. During remissions of asthma, normal spirometric values, such as those in our two asthmatic patients, may be observed even when subtler abnormalities of pulmonary function are detected by other techniques (47). Our finding of small-airway obstruction in half the patients with allergic rhinitis is consistent with previous reports indicating that as many as 13% may have diminished expiratory flows (22), with a magnitude that is intermediate between those of normals and asthmatics (48) and sufficient to explain exercise-induced air trapping (49). Others have reported that increased airway resistance is due to large-airway narrowing in allergic rhinitis (21, 50).

Responses to methacholine in our group were varied and scattered, disproving our hypothesis that they would exhibit a common pattern even if responses did not reach the cutoff criteria for definition of airway hyperreactivity. Half of the patients showed unequivocal bronchoconstriction, whereas the other half did not. The group showing bronchoconstriction consisted of two patients with asthma, one with allergic rhinitis, one with a family history of asthma, and three others apparently lacking any bronchoconstrictor-determining characteristic. Exaggerated responses to methacholine in the asthmatics in this series, one of whom had a positive methacholine test, are expected (20, 21) and need not be related to ACEI-induced cough. The bronchoconstrictor response to methacholine in the patient with allergic rhi-

nititis is consistent with previous reports of exaggerated responses to histamine (28, 48) and methacholine (22) in these patients. However, three other subjects in our study had allergic rhinitis but did not develop bronchoconstriction after methacholine. Enhanced responses to this agent have also been reported in relatives of atopic patients (51). However, only one of the two patients with a family history of asthma exhibited significant bronchoconstriction in response to methacholine inhalation.

Two of the patients whose bronchoconstrictor responses to methacholine were unexplained were being treated with NSAIDs. This makes their responses even more unexpected, since prostaglandins augment airway reactivity (27), and NSAIDs would have been expected to diminish it. Whether verapamil, given to the third patient, could have affected his responses is unclear because the effect of calcium channel blockers on airway reactivity is controversial (29). The combination of ACEIs and β blockers augments airway reactivity (18), whereas the use of α 1 antagonists decreases it (28). However, none of the patients in this series were taking these agents for the management of hypertension. Finally, we did not find that the group of patients with unequivocal bronchoconstriction in response to methacholine was older or had a higher prevalence of left ventricular dysfunction. Both these characteristics have been found to be related to airway hyperreactivity (26, 51).

In conclusion, we were unable to find a common pattern of airway responses to methacholine in a group of hypertensives with ACEI-induced cough. Moreover, individual responses did not seem to be accounted for by the patients' other illnesses or therapies, although the small number of patients in these subgroups does not permit us to draw definite conclusions about this issue.

Our data support the view that responses to methacholine, in a group of patients with ACEI-induced cough selected without regard to the presence or absence of allergic disorders, disclose a normally distributed continuum. Because it is known that bronchial responses to inhaled histamine are unimodally distributed in an unselected population (52), it could be argued that unimodal distribution of methacholine responses in our hypertensive patients is also the expected, or normal, observation. We cannot speculate about this, however, because we did not study comparison groups of hypertensives without ACEI-induced cough or not treated with ACEIs. Instead, we can conclude that if an abnormality in airway function underlies the development of ACEI-induced

cough in some patients with essential hypertension, this is not detectable by study of sensitivity to cholinergic stimuli (2, 12, 13). Prostaglandins (9), bradykinin (7, 10), and substance P (53) are other putative mediators of ACEI-induced cough because ACEIs increase the synthesis of prostaglandins and impair the degradation of the two peptides. Therefore, the possibility of specific airway reactivity to these substances, in patients with ACEI-induced cough, remains to be studied in a direct manner, with methods that permit evaluation of responses at lower and upper (38) airways.

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Psoriatic Arthritis



Psoriatic arthritis occurs in approximately 7% of patients with psoriasis. Several types of psoriatic arthritis occur, and many patients with the disorder have associated changes of fingernails and toenails. Only a small proportion of patients will develop the severe deforming arthritis shown in this figure.—Donald Rudikoff, M.D., and Mark Lebwohl, M.D., Department of Dermatology, The Mount Sinai Hospital

Abstracts

The abstracts presented here, all by principal investigators in the Samuel Bronfman Department of Medicine of the Mount Sinai School of Medicine (which includes the affiliates Bronx Veterans Affairs Medical Center and Elmhurst Hospital Center, both in New York City, and Englewood (NJ) Hospital and Medical Center), were exhibited as posters on the Department of Medicine Thirteenth Annual Research Day, October 31, 1995. Breaks in consecutive abstract numbers by division indicate abstracts by authors who did not grant publication permission.

Research in Medicine 1995 Mount Sinai School of Medicine

Alcohol Research

ALC1. Polyenylphosphatidylcholine (PPC) Attenuates Associated Injury Induced by CCl₄ in Rats and by Alcohol in Baboons by Preventing Hepatic Lipid Peroxidation. S. I. Aleynik, M. A. Leo, X. Ma, M. K. Aleynik, and C. S. Lieber. Alcohol Research Center, Section of Liver Disease & Nutrition, Bronx VA Medical Center and Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: Diets rich in triglycerides containing polyunsaturated fatty acids (PUFA) potentiate alcohol-induced liver injury in rats and promote lipid peroxidation. By contrast, in baboons, PPC, a phospholipid mixture rich in PUFA, prevents alcohol-induced septal fibrosis and cirrhosis.

Methods: To determine whether this paradox reflects a species difference or the type of esterified lipid (triglycerides vs. phospholipids) containing the PUFA, rats were given CCl₄ for eight weeks, resulting, as expected, in liver cirrhosis associated with increased plasma ALT, AST, and a fivefold rise in hepatic F₂ isoprostanes ($p < .001$), a breakdown product of arachidonic acid (measured by GC/MS) which reflects in vivo lipid peroxidation. Supplementation with PPC (3 mg/cal), replacing an equal amount of PUFA-containing triglycerides, attenuated hepatic fibrosis with a concomitant decrease in hepatic collagen accumulation. In addition, PPC totally prevented the increase in F₂-isoprostanes produced by CCl₄ ($p < .01$). There were strong positive correlations between isoprostanes and plasma transaminases ($p < .0001$). To assess this anti-isoprostane effect in another model, baboons fed chronically a liquid diet with alcohol or isocaloric carbohydrates (50% of total energy) were compared to two other groups given the same diets but supplemented with PPC. We reported before that, under these conditions, the alcohol-induced septal fibrosis and cirrhosis is fully prevented by PPC.

Results: We now found that PPC also abolishes the associated twofold rise in hepatic F₂-isoprostanes ($p < .05$), measured in percutaneous needle biopsies. Thus, whereas PUFA given as triglycerides exacerbated the effects of hepatotoxic agents, the opposite was observed with PUFA administered as phospholipids in two different animal species with two distinct models of liver injury. How PUFA in phospholipids oppose rather than promote lipid peroxidation, and whether this is linked to the antifibrotic effect of PPC, is under active investigation in animals as well as humans.

Conclusions: PPC prevents CCl₄- and alcohol-induced lipid peroxidation in rats and baboons, respectively, while it attenuates the associated liver injury.

ALC2. Ranitidine Increases the Bioavailability of Imbibed Alcohol by Accelerating Its Gastric Emptying. I. Amir, N. Anwar, E. Baraona, C. S. Lieber. Alcohol Research and Treatment Center, Bronx VA Medical Center & Mt Sinai School of Medicine (CUNY), New York, NY.

Statement of the Problem: Ranitidine, a commonly used H₂-receptor antagonist, has been found by us (JAMA 267:83-86, 1992) to increase the bioavailability of imbibed alcohol, but the mechanism for this effect remains unknown. At variance with studies in rats, in which ranitidine inhibits gastric alcohol dehydrogenase activity, the results in human stomachs are questionable. However, alcohol bioavailability depends not only on in vitro changes of alcohol dehydrogenase activity but also on the time of exposure of ADH to optimal alcohol concentrations, as determined by changes in gastric emptying. Since ranitidine has significant anticholinesterase activity (which increases gastric motility), we studied its effects on both alcohol bioavailability and gastric emptying of ethanol.

Methods: In 8 normal men, we compared blood ethanol concentrations (assessed by calibrated breathalyzer) after random intravenous and, on a separate day, oral administration of 0.3 g ethanol/kg body weight, pre- and post-ranitidine (300 mg p.o. qhs for 1 week). We calculated bioavailability of ethanol by integration of the Michaelis-Menten function over the entire alcohol curves. To assess concomitant changes in gastric emptying, the oral dose was given as a 10% solution containing 300 μ Ci of an inert, technetium-labeled, soluble marker (diethylene triamine pentacetic acid) to be followed by nuclear scan.

Results: With ranitidine, we found an acceleration of the gastric emptying in 7 of 8 subjects, with 20% shortening of the half-time (64.3 ± 3.4 min without vs 51.8 ± 4.1 with ranitidine; $P < 0.001$ by paired t test). This was associated with an increase in blood alcohol concentrations after oral (22 ± 3 mg/dL without vs 29 ± 4 , with ranitidine; $p < 0.02$), but not after intravenous infusion of ethanol. The increased blood alcohol level was due not merely to a more rapid absorption of alcohol but also reflected an increase in its bioavailability because of an inhibitory effect on first-pass metabolism, which decreased from 107 ± 16 mg/kg body weight before ranitidine to 47 ± 16 after ranitidine ($p < 0.02$) in 7 of the 8 subjects. Despite the disappearance from the stomach of most of the dose by the end of the blood alcohol curves, only $64 \pm 4\%$ reached the systemic blood in the absence of ranitidine and $83 \pm 4\%$ in its presence ($p < 0.02$); thus, the increased rate of gastric emptying produced a parallel rise in bioavailability, probably by decreasing the duration of exposure of gastric alcohol dehydrogenase to optimal concentrations of ethanol. There was an inverse correlation between the changes in the rate of gastric emptying and those in first-pass metabolism of ethanol ($r = 0.857$; $p < 0.01$).

Conclusions: Ranitidine increases both the blood alcohol levels and the bioavailability of imbibed alcohol, at least in part, by accelerating the rate of gastric emptying of ethanol. Thus, patients given ranitidine should be warned of the possibility of an impairment in skills for performing complex tasks, such as driving, when engaged in social drinking.

ALC3. Increased Vulnerability of Women to Alcoholic Liver Injury as Reflected by the Lack of Dicarboxylic Aciduria after Alcohol Consumption. E. Baraona, X. Ma, B. Goozer, C. S. Lieber. Alcohol Research and Treatment Center, Bronx VA Medical Center, Mount Sinai School of Medicine, and Long Island College Hospital, New York, NY.

Statement of the Problem: Women develop alcoholic liver disease more readily than men. One of the possible mechanisms for this gender effect could be a difference in the hepatic response to the metabolic derangements produced by ethanol. An early and sensitive target of alcohol hepatotoxicity is the inhibition of mitochondrial fatty acid oxidation, which might result in hepatic accumulation of potentially deleterious nonesterified fatty acids. We previously found that the alcohol-induced inhibition of mitochondrial β -oxidation was associated with a concomitant induction of cytochrome P450A1-mediated ω -oxidation and did not result in fatty acid accumulation in male rats. Dicarboxylic acids (products of ω -oxidation) can increase the transcription of the cytosolic fatty-acid binding protein, the peroxisomal acylCoA oxidase, and the microsomal P450A1, thereby enhancing alternate pathways for fatty acid disposition, such as microsomal acylglycerol synthesis and ω -oxidation and peroxisomal β -oxidation. However, these protective mechanisms were less efficient in female than in male rats, resulting in a threefold accumulation of fatty acids in the liver of females consuming alcohol.

Methods: To assess whether similar gender differences pertain to alcoholics, we determined the urinary excretion of medium chain dicarboxylic acids (final products of fatty acid ω -oxidation) in 31 recently drinking alcoholics without severe liver disease (24 men and 7 women) and 21 nonalcoholics (12 men and 9 women). Those taking aspirin in the previous two days or with other causes of dicarboxyluria were excluded. Sebacic (C10), suberic (C8), and adipic (C6) acids were measured in urine by gas chromatography/mass spectrometry, and their excretion was expressed per mg creatinine.

Results: In nonalcoholics, there was no gender difference in dicarboxylic acid excretion. By contrast, alcoholic men (but not alcoholic women) developed dicarboxylic hyperaciduria ($P < 0.05$), with a sixfold increase in adipic acid (3.8 ± 0.7 vs 0.6 ± 0.2 ; $P < 0.002$) compared to alcoholic women of similar nutritional status. This was associated with a fivefold increase of the C6:C10 ratio (an index of peroxisomal β -oxidation) in alcoholic men (vs nonalcoholics) and a 50% decrease in alcoholic women.

Conclusions: Men develop enhanced microsomal ω -oxidation and peroxisomal β -oxidation in response to alcohol consumption (as indicated by the dicarboxylic aciduria), whereas the lack of this compensatory response in women could promote deleterious accumulation of fatty acids in the liver. This may contribute to the propensity of women to develop a more severe alcoholic liver injury than men.

ALC4. A Comparison of High vs. Standard Dose of Hepatitis B Vaccine in Alcoholic Patients: A Randomized Clinical Trial. P. Basu, A. S. Rosman, K. Galvin, C. S. Lieber. Alcohol Research and Treatment Center, Bronx VA Medical Center, and Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: Previous studies have reported that alcoholic patients have a high risk of contracting hepatitis B viral infection; however, vaccination trials in alcoholics have reported a low seroconversion rate using standard doses of hepatitis B vaccine.

Methods: We therefore conducted a randomized, double-blind trial comparing the standard dose (20 micrograms at 0, 1, and 6 months) to a high one (40 micrograms at 0, 1, 2, and 6 months) of recombinant hepatitis B vaccine (Engerix-B, generously supplied by SmithKline Beecham Pharmaceuticals, Philadelphia, PA). Ninety-seven male alcoholics (mean age $\pm$ SEM, 51.4 ± 1.2 years; 24 white, 33 Hispanics, 40 Afro-American) who were seronegative for hepatitis B virus were randomized to receive either standard ($N = 51$) or high ($N = 46$) dose vaccine. Patients were monitored for relapse of drinking using self-report, serial serum carbohydrate deficient transferrin (generously supplied by Kabi Pharmacia Diagnostics, Piscataway, NJ), and collateral verification (when available). The final anti-HBs titer was ob-

tained 12 months after the first vaccine dose; a seroconversion was defined as a titer greater than 10 mIU/ml.

Results: Eighty-nine subjects completed the study (5 were lost to follow-up, 2 withdrew, and 1 died). Nine of the subjects who completed the study had clinical or pathological evidence of cirrhosis. During the study, there were 46 documented relapses of drinking (13 required hospitalization for detoxification); each treatment group had 23 cases. Thirty-one out of 42 (74%) of patients receiving the high-dose regimen seroconverted, compared to 21 of 47 (45%) in the standard dose group ($P < 0.01$). The mean anti-HBs titer of the high-dose group was significantly greater than the standard-dose group (69.4 vs 37.9 mIU/ml, $P = 0.01$ by Mann Whitney U test). Logistic regression demonstrated a significant effect of the vaccine dose on seroconversion ($P = 0.01$) but not for the other variables such as race, age, drinking during the study, serum albumin, serum creatinine, arm muscle circumference, and cirrhosis (diagnosed by biopsy or clinical signs).

Conclusions: A high-dose regimen of hepatitis B improves the serologic response in alcoholic patients. This regimen (currently recommended for hemodialysis patients) should now also be considered for patients with a history of alcoholism.

ALC5. The Prevalence of *Helicobacter pylori* Is Increased in Cirrhotic Patients with Hepatic Encephalopathy and Eradication Therapy Appears to Ameliorate Symptoms. B. M. Dasani, S. H. Sigal, C. S. Lieber. Alcohol Research and Treatment Center, Bronx VAMC and Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: Elevated blood ammonia levels resulting from impaired hepatic clearance and portosystemic shunting are frequently implicated in the pathogenesis of hepatic encephalopathy (HE). Protein breakdown by colonic bacteria is considered to be the main source of the ammonia. However, the stomach in individuals colonized by urease producing *Helicobacter pylori* (Hp+) is an alternative site.

Methods: To determine whether Hp contributes to the development of HE, 20 stable, nonazotemic (BUN < 25 , stable diuretic doses), ambulatory cirrhotic patients (14 alcoholic [A], 5 A + HCV, 1 HCV) with HE (presence of asterixis, day/night reversal, and/or abnormal psychometric testing including trail test time, TT) were compared to noninfected cirrhotics (Hp-) (1 A, 3 A + HCV, 2 HCV). Patients in both groups were similar in terms of liver tests, evidence of portal hypertension, and blood ammonia levels.

Results: The only statistically significant differences between the two groups were age (58.7 ± 2.1 vs 42.3 ± 3.6 years, $p = .001$), presence of Hp (85 vs 17%, $p < .005$), and gastric juice analysis for urease activity (the extent to which gastric juice urea derived from blood is converted into ammonia), which included gastric ammonia level ($4.58 \pm .55$ vs $1.93 \pm .64$ mM, $p < .05$) and the urea/ammonia ratio ($.37 \pm .12$ vs $1.45 \pm .43$, $p < .05$). In 7 patients followed for 35.6 ± 7.7 days, the degree of HE was unchanged (TT 47.1 ± 4.3 vs 46.0 ± 6.0 sec, $p = .76$). In contrast, 7 patients colonized with Hp experienced improvement in symptoms following eradication therapy (amoxicillin, omeprazole) with resolution of day/night reversal (4 of 4). In addition, there was a trend toward improved TT (60.3 ± 13.5 vs 42.1 ± 4.9 sec, $n = 7$, $p = .085$) which was sustained for up to 2 months, suggesting that this effect was due to Hp eradication. These results are consistent with a role for Hp in the pathogenesis of HE. To assess a possible contributory effect of amoxicillin on colonic bacteria, Hp- patients with HE are currently being studied.

Conclusions: Hp is strongly associated with chronic HE, and Hp eradication appears to improve symptoms and could be considered in the management of HE.

ALC6. Aspirin Raises Blood Alcohol Concentration by Inhibition of Alcohol First-Pass Metabolism. R. Thomas Gentry, Imran Amir, and Charles S. Lieber. Department of Medicine, Mount Sinai School of Medicine, Alcohol Research and Treatment Center, Bronx VA Medical Center.

Statement of the Problem: Previously we showed that aspirin increases blood alcohol concentration (BAC) after postprandial alcohol consumption (Roine et al, JAMA 264:2406-8, 1990), and the present studies were designed to determine whether this was due to accelerated gastric emptying, a slower rate of alcohol elimination, or the inhibition of alcohol first-pass metabolism (FPM).

Methods: To assess the effect of aspirin on gastric emptying, nine healthy men were each given a drink containing 0.3 g alcohol (10% w/v in orange juice) and ^{99m}Tc -DTPA (300 μCi) one hour after a standard meal. Each subject was tested both without and with aspirin (1 g taken with the meal), and gastric emptying was monitored by gamma camera for at least two hours.

Results: Compared to control, aspirin did not significantly affect the half-time of ^{99m}Tc -DTPA loss from the stomach (from 65.5 ± 5.4 min without, to 71.3 ± 6.5 min with aspirin), demonstrating that the aspirin-induced higher BACs are not attributable to faster gastric emptying. Although aspirin significantly increased peak BACs and the mean area-under-the-curve after orally administered alcohol, it did not affect BAC curves after the intravenous administration of alcohol, indicating it had no effect on the systemic elimination of alcohol. There was, however, a significant decrease in alcohol FPM (from 106 ± 24 to 65 ± 19 mg/kg, $p < 0.05$, paired t -test), as indicated by pharmacokinetic analysis of blood alcohol curves obtained by both the intravenous and oral routes.

Conclusions: Thus, increased BAC after aspirin is not due to accelerated gastric emptying or the slower systemic elimination of alcohol, but is the consequence of decreased FPM, which is consistent with the inhibition of gastric alcohol dehydrogenase activity previously shown.

ALC7. The Combined Effects of Cerulein and Chronic Ethanol Feeding on the Rat Pancreas. M. A. Korsten, P. S. Haber, J. S. Wilson, C. S. Lieber. Alcohol Research and Treatment Center, VA Medical Center, Bronx, NY, Mount Sinai School of Medicine, New York, NY, and Gastrointestinal Unit, Prince of Wales Hospital, Randwick, NSW 2031, Australia.

Statement of the Problem: A number of ethanol-induced changes have been described in the pancreas which may render it more susceptible to injury. These include increased fragility of both pancreatic lysosomes and zymogen granules and increased digestive enzyme content. These effects may predispose the pancreas to autodigestion via the intracellular activation of digestive enzymes by lysosomal enzymes. Since infusion of supramaximal doses of cerulein (a CCK analog) is also associated with lysosomal fragility (and pancreatic injury), we wondered whether chronic ethanol administration would potentiate the injurious effects of cerulein administration.

Methods: To explore this issue, the severity of pancreatitis was compared in three groups of rats following intravenous infusion of supramaximal doses of cerulein (5 $\mu\text{g/kg/hr}$ for 5 hours): (1) rats pair-fed nutritionally adequate liquid diets containing 35% ethanol; (2) rats fed a liquid diet containing an amount of dextrose isocaloric to that of ethanol; and (3) chow-fed controls. At the end of the feeding period, rats were killed before and after the administration of a supramaximal dose of cerulein. The severity of pancreatitis after cerulein was determined by pancreatic weight (an index of pancreatic edema), pancreatic histology (H&E staining), and serum amylase.

Results: The pancreatic weight of rats given cerulein was similar in ethanol-fed, pair-fed dextrose controls, and chow-fed controls. The histologic severity of pancreatitis was also similar in the three groups of rats. Plasma amylase activity was increased in animals after cerulein, but this increase was significantly less in the alcohol-fed animals. In addition, we sought to define other biochemical parameters that might precede evidence of obvious injury. To this end, we further assessed the effects of cerulein infusion and chronic ethanol feeding on pancreatic levels of cathepsin B, the subcellular distribution of cathepsin B, and the fragility of the lysosomal fraction. For animals killed in the fed state (no cerulein), the activity of cathepsin B was higher in alcohol-fed animals than in pair-fed controls and chow-fed animals. Cerulein infusion led to a marked redistribution of cathepsin B activity from the lysosomal enriched fraction to the zymogen granule enriched

fraction. However, this redistribution was similar in ethanol-fed and control animals. To assess lysosomal fragility, pancreatic homogenates were incubated for periods up to 135 minutes. Activity of cathepsin B was determined in the supernatant after resedimentation and expressed as % of total. Lysosomal fragility induced by cerulein infusion was similar in ethanol-fed and control groups (53.0 ± 10.3 vs. $55.0 \pm 4.7\%$ cathepsin B in supernatant at 135 mins, $p > 0.1$).

Conclusions: Chronic ethanol administration per se results in a redistribution of cathepsin B activity toward the zymogen granule-enriched fraction in alcohol-fed rats compared to their pair-fed controls. However, ethanol feeding does not increase the severity of pancreatitis induced by hyperstimulation with cerulein. The present study does not support the concept of synergism between chronic alcohol consumption and other causes of pancreatic injury.

ALC8. Ethanol Induces Cytochrome P4502E1 Expression in Rat Kupffer Cells. T. Koivisto, V. M. Mishin, K. M. Mak, P. A. Cohen, C. S. Lieber. Departments of Medicine and Cell Biology/Anatomy, Mount Sinai School of Medicine, and Alcohol Research and Treatment Center, Bronx VA Medical Center, New York, NY.

Statement of the Problem: Cytochrome P4502E1 (2E1) is an ethanol-inducible enzyme which has been associated with the development of alcoholic liver injury. Alcohol is known to alter Kupffer cell functions, including phagocytosis, cytokine production, and oxygen radical formation, but the mechanisms underlying these changes are unknown. One potential mediator is 2E1. The purpose of this study was to determine whether 2E1 is inducible by ethanol, not only in hepatocytes, but also in Kupffer cells, and in the affirmative, to assess whether this induction is accompanied by an increased activation of 2E1 dependent-monooxygenase.

Methods: Adult male Sprague-Dawley rats were pair-fed Lieber-DeCarli liquid diets containing 36% of calories as ethanol, or an isocaloric amount of dextrin for 3 weeks. Kupffer cells were isolated from collagenase-perfused livers by isopycnic centrifugation in Percoll and selective adherence onto glass coverslips. Hepatocytes were also isolated. The purity of isolated Kupffer cells was 85% as assessed by endogenous peroxidase activity staining. Parenchymal cell contamination was negligible.

Results: Immunohistochemical studies revealed that in vivo 2E1 was localized in the endoplasmic reticulum (ER) of Kupffer cells and hepatocytes and that it is also present in isolated Kupffer cells. Immunoblotting experiments performed with the S9 fraction showed that ethanol consumption caused a sevenfold increase in 2E1 content in both Kupffer cells and hepatocytes. When expressed per mg S9 protein, the content of 2E1 in Kupffer cells was more than 10 times lower than in hepatocytes. Ethanol feeding increased p-nitrophenol hydroxylation rates fivefold in Kupffer cells and sevenfold in hepatocytes, demonstrating that the induced 2E1 was catalytically active. This reaction was inhibited by greater than 80% with an anti-2E1 IgG in both types of cells.

Conclusions: Kupffer cells constitutively express 2E1. Chronic ethanol consumption causes a marked increase of a catalytically active 2E1. This induction of 2E1 after ethanol consumption is likely to cause an increased production of acetaldehyde and lipid peroxidation, which may affect cytokine production. This may promote fibrogenesis, thereby contributing to the development of liver injury.

ALC9. Hepatic Effects of β -Carotene Beadlets and/or Ethanol. M. A. Leo, S. Aleynik, M. Aleynik, C. S. Lieber. Alcohol Research Center, Section of Liver Disease and Nutrition, Bronx VA Medical Center, and Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: Several epidemiologic studies revealed a favorable effect of dietary β -carotene (βC) on the incidence of various cancers, whereas supplementation with βC beadlets had the opposite result on pulmonary cancer in smokers (NEJM 330:1029, 1994) and

potentiated alcohol-induced hepatotoxicity in baboons (Leo et al., *Hepatology* 15:883, 1992).

Methods: To determine the relative role of ethanol, β C, and the beadlet carrier, rats were given our standard liquid diet containing 6 IU/cal retinyl acetate, with or without beadlet carrier, or a diet devoid of vitamin A but containing β C, either 11 μ g/cal (an amount considered equivalent to the vitamin A in the normal diet), 28 μ g/cal, or 56 μ g/cal, given either as pure β C or as β C in beadlets.

Results: Isocaloric substitution of carbohydrates with ethanol reduced hepatic vitamin A by 80%, as we reported before, and such a depletion was now also observed when β C was used as vitamin A precursor. By contrast, ethanol increased hepatic β C content, and the absolute levels reached (with or without ethanol) were much higher with β C in beadlets, which markedly enhanced β C bioavailability. Thus, whereas alcohol promoted hepatic depletion of vitamin A, it had the opposite effect on β C, suggesting an interference by alcohol in the conversion of β C to vitamin A. Interestingly, when beadlet carrier was given without ethanol, there was a significant increase in plasma glutamic dehydrogenase (GDH) activity, a mitochondrial enzyme, with associated mitochondrial lesions by electron microscopy. Furthermore, beadlets also resulted in a proliferation of the membranes of the smooth endoplasmic reticulum. Moreover, there was also an apparent increase in hepatic F_2 isoprostanes, an index of endogenous lipid peroxidation, measured by GC-MS, despite a concomitant rise in hepatic vitamin E and the increase in β C (see above).

Conclusions: β -Carotene alone is not a good precursor of vitamin A, especially in the presence of ethanol. Its bioavailability is improved by beadlets, but in view of their observed side effects in rats, studies are now needed to determine to what extent these also occur in humans.

ALC10. Cytochrome P4502E1 Content and Activity in Rat Kidney Microsomes after Chronic Alcohol Consumption. V. Mishin, T. Koivisto, C. S. Lieber. Alcohol Research and Treatment Center, Bronx VA Medical Center, and Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: The ethanol-inducible cytochrome P4502E1 (CYP2E1) actively converts chemical compounds such as ethanol and acetaminophen to toxic products (Garro, Lieber, 1990). These products have been linked to injury in the liver and possibly in the kidney. However, we are unaware of any report that measures CYP2E1 content in the kidney microsomes after chronic ethanol feeding. Additionally, the metabolism of ethanol, chlorzoxazone and p-nitrophenol, which are typical substrates of CYP2E1 and which would demonstrate its activity, have not been determined in rat kidney microsomes to date.

Methods: Therefore, male rats were pair-fed liquid diets containing 36% as ethanol (ethanol-fed) or carbohydrates (controls) and liver and kidney microsomes were prepared. Specific polyclonal antibodies against hamster CYP2E1 were used as the primary antibody in the Western-Light chemiluminescent detection system (Tropix, Inc., Bedford, MA) after SDS-PAGE (Laemmli system) and for immunoinhibition of the enzymatic reactions. The formation of 6-OH chlorzoxazone was detected as described (Peter et al. 1990). The assay of ethanol oxidation was carried out by measurement of acetaldehyde formation using a head-space gas chromatograph (Ohnishi, Lieber, 1977). The assay of p-nitrothechol formed during p-nitrophenol hydroxylation was conducted with an HP1090 integrated system equipped with BAS LC-4A electrochemical detector. A glassy carbon working electrode was set at +0.7 V against an Ag/AgCl reference electrode. A Beckman Ultrashere ODS 5 μ m (4.6 mm $\times$ 25 cm) column and the mobile phase, 25% acetonitrile and 0.1% trifluoroacetic acid was used.

Results: There was a fourfold increase of the CYP2E1 content in the kidney microsomes of ethanol-fed rats as compared to control animals. The CYP2E1 content was 27 times greater in the liver microsomes than that in the kidney microsomes of ethanol-fed rats. Chronic ethanol feeding affected the rate of metabolism of CYP2E1-dependent reactions with a 6–7-fold increase in the rate of p-nitrophenol and chlorzoxazone hydroxylation and of ethanol oxidation in the kidney microsomes. This metabolism was significantly inhibited (80%) by polyclonal antibodies specific against CYP2E1 in ethanol-induced kidney and liver microsomes.

Conclusions: CYP2E1 is the major, if not the only, catalyst among the other cytochrome P450 forms of p-nitrophenol and chlorzoxazone hydroxylation as well as ethanol oxidation in the kidney and liver microsomes of rats. The catalytic activity of CYP2E1 per unit of CYP2E1 protein is higher in rat kidney than in rat liver after chronic alcohol feeding. This greater activity could be linked to the kidney pathology associated with drug intake and environmental pollutants in chronic alcohol abuse.

ALC11. The Gastric/Blood Urea Ratio: A New Diagnostic Test for *Helicobacter pylori* Detection. A. Mokuolu, S. H. Sigal, C. S. Lieber. Bronx VA Medical Center, and Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: A noninvasive assay for the detection of *Helicobacter pylori* (Hp) that is inexpensive, sensitive, and readily available is currently lacking. Urease activity (hydrolysis of urea to ammonia, UA) is the most characteristic feature of Hp and is employed in its diagnosis by the CLO test and urea breath test (UBT). However, direct measurement of the extent to which gastric urea (derived from the blood) is converted into ammonia should provide comparable if not better results.

Methods: To determine if gastric juice analysis can serve as an indicator of UA, gastric juice was collected in 28 patients with dyspepsia, and UA determined by the ratio of urea in gastric juice to blood (G/B-U) and the gastric urea/ammonia ratio (U/A).

Results: Fifteen patients (7 ulcers) were Hp+ by either CLO test (13) or initial histologic review (11), and 13 patients (3 ulcers) were Hp-. Levels of urea were lower and ammonia higher in the Hp+ than in the Hp- patients ($42 \pm .09$ vs $3.49 \pm .75$ mM and 6.72 ± 1.26 vs $1.84 \pm .35$ mM, respectively; $p < 0.01$) but overlapped. G/B-U was $.09 \pm .02$ and $.53 \pm .05$ and U/A $.11 \pm .04$ and 3.96 ± 1.79 in Hp+ and Hp- patients, respectively ($p < .001$). Sensitivity of the CLO test and the initial histologic review were 87% and 73%, respectively. Using values of less than .2 and .4 for G/B-U and U/A for Hp+, the sensitivities and specificities for G/B-U were 93% and 100% and for U/A 93% and 92%, respectively. In one ulcer patient with negative CLO test, the initial histologic review failed to detect Hp. However, due to strong UA (U/A .10, G/B-U .11), infection was suspected, and intensive scrutiny of the biopsy revealed the presence of few Hp organisms. Thus, the G/B-U, which can be obtained nonendoscopically by orogastric intubation, is a sensitive and specific approach for the detection of Hp infection. It is cheaper and less invasive than tests requiring endoscopy and more readily available than the UBT. It is also preferable to serology, which does not indicate active infection. Previous observations indicate that the ratio is applicable in uremic patients (JCI 1959;38:1271–7), and preliminary data suggest that this test can be utilized in the follow-up of treated patients to confirm Hp eradication.

Conclusions: The G/B-U test is the simplest and cheapest and could be the most accurate means of detecting Hp infection. Its wider validation and application is now indicated.

ALC12. Serum Carbohydrate-Deficient Transferrin (CDT): Mechanism of Its Increase after Alcohol Consumption. Y. Xin, J. M. Lasker, C. S. Lieber. Section of Liver Disease and Nutrition, Alcohol Res Ctr, Bronx VA Medical Center and Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: Carbohydrate-deficient transferrin (CDT) is now considered to be the most sensitive and specific biological marker of alcohol abuse. However, the mechanism by which chronic alcohol consumption causes an elevation of CDT levels in serum is still not fully understood.

Methods: Therefore, we fed 8 pairs of male rats a nutritionally adequate liquid diet containing either alcohol (36% of energy) or isocaloric dextrose (control) for 4 weeks, after which blood and liver samples were obtained.

Results: Serum CDT content in alcohol-treated rats increased by 45% ($p < 0.05$) as assessed with an isoelectric focusing-Western blot method, thereby mimicking the clinical condition. In particulate fractions (plasma membranes) prepared from the liver samples, the activity of sialidase was increased 1.62-fold ($p < 0.05$) in ethanol-fed animals compared to their corresponding controls. In contrast, in rats fed ethanol, the activities of sialyltransferase, galactosyltransferase, and *N*-acetylglucosamine transferase, which are glycosyltransferases involved in transferrin carbohydrate side chain synthesis, were diminished by 24% and 40% ($p < 0.05$), 23% and 51% ($p < 0.05$, 0.001), and 20% and 26% ($p < 0.05$) in total liver homogenates and Golgi fraction 1, respectively, when expressed as units/100g body weight. These enzymes were also significantly less active in hepatic Golgi fractions 2 and 3. The depression of the transferase activities in ethanol-fed rats appeared to be due, at least in part, to enzyme inactivation by acetaldehyde, whereas ethanol itself was without effect. Similar results were obtained in humans: 5 alcohol abusers were found to exhibit a 23% decrease in hepatic sialyltransferase and a 41% increase of sialidase activities, respectively, when compared to 3 nondrinking subjects.

Conclusions: The increased activity of sialidase in liver particulate fractions, combined with the decrease in transferrin glycosyltransferases in Golgi fractions, mediated by ethanol (or acetaldehyde derived from ethanol) most likely accounts for the enhanced serum CDT in response to chronic ethanol consumption in rats as well as in humans.

ALC13. Molecular Cloning of *ADH7* Encoding Human Class IV (σ) Alcohol Dehydrogenase (ADH) and the Organ Distribution of Its Expression. H. Yokoyama, E. Baraona, and C. S. Lieber. Alcohol Res Ctr, Bronx VA Medical Center and Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: Human class IV (σ) ADH is present in the gastric mucosa and may diminish the amount of absorbed alcohol. We recently cloned the cDNA for this isozyme and determined its full structure (BBRC 203:219, 1994). The aim of this study was to examine the structure of the gene encoding σ -ADH (*ADH7*) and the distribution of its organ expression.

Methods: Intron 2 of *ADH7* was first amplified by PCR from a genomic DNA library in bacteriophage P1, constructed from a white person. The library was then screened with the PCR amplicon as a probe, resulting in two clones carrying the full length *ADH7*.

Results: Fluorescence in situ hybridization analysis displayed that *ADH7* was located on human chromosome 4q23-24, close to *ADH1-5* (4q21-25). *ADH7* has 9 exons and 8 introns which span about 22 kb, a structure similar to that of *ADH1-5*. The nucleotide sequences of the exons encoding 374 amino acids were identical to the reported cDNA sequence of σ -ADH and revealed a significant difference in exon 7 when compared to that of recently reported *ADH7* cloned from a Japanese (S. Yokoyama et al., FEBS letters 351:411, 1994).

To examine the frequency of the mutation, restriction fragment length polymorphism analysis with *Ava* II and *Mae* III for PR amplicon of the exon 7 was performed in 7 Japanese and 7 white subjects and showed that the change reported by S. Yokoyama et al. was rare in both groups. Northern hybridization analysis with a specific probe for σ -ADH showed that this gene is expressed predominantly in the stomach, whereas class I ADH was abundantly expressed in several organs.

Conclusions: The *ADH7* upstream had sequences which are compatible with glucocorticoid and estrogen response elements, suggesting that these hormones are involved in the regulation of the gene expression. The lack of CG rich sequence and presence of TATA and CAAT boxes in this region may reflect the organ-specific but not ubiquitous expression of this gene. The lack of hepatocyte nuclear factor in the region may account for the fact that this gene is not expressed in the liver, since this factor has been implicated in the liver expression of *ADH1-3*.

Cardiology

C1. Safety and Efficacy of OKT3 Induction in Cardiac Transplantation. Srihari S. Naidu, Billie Fyfe, Mary Courtney, Rhodora Correa, Steven Lansman, Alan Gass. Division of Cardiology, Departments of Medicine, Pathology, and Cardiothoracic Surgery, The Mount Sinai Hospital, New York, NY.

Statement of the Problem: OKT3 induction therapy remains controversial. While OKT3 induction may provide a safer immediate post-transplant period by delaying time to first rejection, an association with increased incidence of infection has been noted, and use of the drug may not decrease overall rejection frequency. In addition, it has been used to delay the administration of cyclosporine A in high-risk patients. Many transplant centers have switched to short-course OKT3 in an attempt to maintain the positive effects while minimizing the negative.

Methods: To determine the benefit of OKT3 induction, we retrospectively divided 67 adult transplant patients into those who received no ($n = 17$), short-course (5 to 9 days; $n = 25$), and long-course (10 to 14 days; $n = 25$) induction therapy. High-risk patients, defined as those with operative hemodynamic compromise and renal or hepatic insufficiency, were preferentially targeted for induction. Triple-drug immunosuppression, age, and gender did not differ significantly among the groups. Time to first rejection was defined as the duration (days) until an ISHLT Grade $\geq$ IA was seen on endomyocardial biopsy. A rejection episode was defined by an ISHLT Grade $\geq$ IA, lasting until an ISHLT grade 0 on subsequent biopsies. Infection was defined as either a confirmed diagnosis or a clinical diagnosis subsequently treated. Except for one patient in the no-induction group who died of repeated infection within four months, only patients who survived for the 6-month period were analyzed for infection and rejection frequency.

Results: Time to first injection was calculated for all patients.

OKT3 (days)	First rejection (days)
0 ($n = 17$)	45.75 $\pm$ 10.3 ($n = 16$)
5 to 9 ($n = 25$)	62.17 $\pm$ 12.7 ($n = 24$)
10 to 14 ($n = 25$)	32.88 $\pm$ 04.1 ($n = 24$)
Infections/6 mo.	Rejections/6 mo.
1.19 $\pm$ 0.28 ($n = 16$)	1.93 $\pm$ 0.21 ($n = 15$)
1.17 $\pm$ 0.22 ($n = 24$)	1.92 $\pm$ 0.17 ($n = 24$)
1.74 $\pm$ 0.36 ($n = 23$)	1.96 $\pm$ 0.17 ($n = 23$)

No significant difference was found in time to first rejection episode, rejection frequency, perioperative mortality, renal failure, or six-month survival. No significant difference was found in frequency of infection, although a trend toward a greater incidence was seen with long-course vs. short-course induction ($p \leq 0.18$).

Conclusions: Although OKT3 induction appears to be of little or no benefit when compared to no induction, such therapy appears effective in maintaining excellent survival and low morbidity in a presumably compromised, high-risk group.

C2. Cardiac Perfusion Imaging and Referral for Catheterization in Octogenarians. M. J. Henzlova, J. A. Diamond, J. Machac. Mount Sinai Medical Center, New York, NY.

Statement of the Problem: Current practice guidelines (ACC/AHA Task Force) do not differentiate on the basis of age. The purpose of our study was to evaluate referral patterns for cardiac catheterization (cath) in the very old in a tertiary urban medical center.

Results: Between 1/93 and 12/94, 223 octogenarians underwent SPECT myocardial perfusion stress imaging: 132 were screened for CAD (Gr I), 91 had known CAD (Gr II). Within 3 months, 44 pts underwent cath (IA + IIA), 179 pts did not (IB + IIB). In the same time period, 1536 pts <65 yrs old were screened for CAD, 132 underwent cath (Gr IIB):

Group	I	II	p	IA + IIA
N	132	91	—	44
Age	83 + 3	83 + 3	ns	83 + 3
M/F	55/77	52/39	0.03	29/15
Sev	1.6	2.4	<0.01	2.7
Ter	1.4	1.9	<0.01	2.1
Isch	67	78	ns	93
Norm	46	16	<0.01	5

IB + IIB	p	IA	III	p
179	—	28	134	—
83 + 3	ns	83 + 3	54 + 8	<0.001
78/101	0.01	19/9	79/55	ns
1.7	<0.00	12.7	2.3	0.01
1.5	<0.00	12.1	1.9	ns
66	<0.001	100	96	ns
41	<0.001	4	7	ns

Sev = index of SPECT defects severity, Ter = # of territories with defects, Isch = % of pts with SPECT ischemia, Norm = % of pts with normal SPECT.

Conclusions: 1. Perfusion abnormalities are less severe in octogenarians screened for CAD than in those with established CAD. 2. Referral for cath in pts screened for presence of CAD is similar in octogenarians and their younger counterparts. 3. The cath referral is driven by SPECT results, not by patient's age.

C4. A Study of Myocardial Thallium-201 (TL-201) Redistribution and Rejection Kinetics with a Clinical and Computer Model. J. Machac, S. Lerakis, M. K. Ali, N. Cho, S. Vallabhajosula. Mount Sinai Medical Center, New York, NY.

Statement of the Problem: We wished to study the effect of low plasma Tl-201 levels on myocardial Tl-201 redistribution and reinjection kinetics in ischemic disease.

Methods: Measurements of plasma and myocardial Tl-201 kinetics were obtained over 24 hours in 30 subjects after either exercise (8) or dipyridamole (22) stress. Plasma Tl-201 kinetic components were correlated with myocardial washout kinetics. A compartmental model was used to study the effects of plasma Tl-201 kinetics in combinations of coronary stenosis and tissue injury.

Results: Clinical measurements showed that a rapid fall in plasma Tl-201 levels after injection and low steady state Tl-201 levels correlated with faster myocardial washout ($p < 0.01$). Computer model simulation showed that low plasma Tl-201 levels caused increased and accelerated redistribution in viable myocardium. Simulated reinjection at rest caused a worsening of Tl-201 defects in regions with critical stenoses. Reinjection led to transient improvement in relative uptake in regions with impaired myocardial retention and noncritical stenoses. This benefit was more notable with low plasma Tl-201 levels.

Conclusions: These results revise some commonly held beliefs, explain many empirical observations, and help in the understanding of the use of Tl-201 redistribution and reinjection imaging of injured myocardium.

C5. SM-20 Is a Novel Growth-Factor-Response Gene Developmentally Regulated in Skeletal and Cardiac Muscle. L. Tsao, S. Wax, M. Moschella, M. Taubman. Mount Sinai Medical Center, New York, NY.

Statement of the Problem: We have previously reported the identification of SM-20, a novel growth-factor-responsive gene in vascular

smooth muscle cells (SMC). SM-20 mRNA, which has an open reading frame encoding a 355 amino acid protein, was found in smooth, skeletal, and cardiac muscle. We now report the identification and characterization of SM-20 protein.

Methods: An affinity purified polyclonal antibody was raised against the bacterially expressed protein.

Results: Western blot analysis of rat aortic smooth, skeletal, and cardiac muscle revealed a single major protein species migrating at ≈ 40 kD. The cDNA and amino acid sequences were unique among all other mammalian sequences currently in the GenBank. Immunohistochemistry revealed that SM-20 protein is specific to SMC in the normal and atherosclerotic vessel wall of human coronary arteries. To examine its regulation in sarcomeric tissue, SM-20 mRNA and protein were assayed in mouse C₂C₁₂ myoblasts. In proliferating mouse C₂C₁₂ myocytes SM-20 mRNA and protein were present only at low levels. Induction of differentiation by 3% horse serum was associated with a marked increase of SM-20 mRNA levels. Immunostaining of growing myoblasts showed minimal staining. However, the differentiated cells showed marked SM-20 protein in all developing myotubes but not in unfused myoblasts. Consistent with these findings, SM-20 mRNA was not detected in the fusion-defective myocyte cell line BC3H1. Northern blot analysis revealed low levels of mRNA in the fetal rat heart with increased levels in the adult and hypertrophied hearts. To examine the regulation of SM-20 during development, immunohistochemistry was performed on sections of mouse embryos. SM-20 antigen was detected at low levels in the heart and somite pairs of 9.5 day embryos with a rostral to caudal distribution gradient. SM-20 protein was detected in skeletal and smooth muscle as well as heart at 10.5 days and increased in intensity in these tissues throughout the rest of development.

Conclusions: SM-20 encodes a novel protein which is developmentally regulated in embryos and induced during differentiation of skeletal myoblasts. Thus, SM-20 may play a role in the development of heart and skeletal muscle.

C6. Tissue Factor Pathway Inhibitor (TFPI) Reduces Thrombus Formation on Lipid-Rich Human Atherosclerotic Plaque. Juan J. Badimon, Maddalena Lettino, Vincenzo Toschi, Richard Gallo, John T. Fallon, Yale Nemerson, Lina Badimon, James H. Chesebro, Valentin Fuster. Cardiovascular Biology Research Laboratory, Cardiovascular Institute, The Mount Sinai Hospital, New York, NY.

Statement of the Problem: Thrombus formation on disrupted atherosclerotic plaques plays a key role in the onset of acute coronary events. We have previously reported that atheromatous core is the most thrombogenic component of human atherosclerotic plaques. The presence of tissue factor (TF) in human atheromatous (AT) plaques appears to account for this thrombogenicity and has been reported. After spontaneous or angioplasty-induced rupture of lipid-rich AT plaques, TF is exposed to flowing blood triggering thrombogenicity. Tissue factor pathway inhibitor (TFPI) is a factor Xa-dependent feed-back inhibitor of the TF-VIIa complex. We have studied the effects of specific TF inhibition by TFPI on thrombus formation triggered by disrupted human AT plaques. The human AT plaques exposed in the chamber fulfill the characteristics of the so-called "vulnerable plaques" histologically defined by the presence of a lipid-rich core.

Methods: Recombinant human TFPI was supplied by CHIRON Corp. Disrupted human AT plaques mounted on the Badimon perfusion chamber were exposed to in vivo heparinized porcine blood (aPTT ratio = 2.0) for 5 minutes. Perfusion was performed at low conditions modeling shear rates typical of mildly stenosed coronary arteries (1690/s). Thrombus formation was evaluated by deposition of ¹¹¹In-labeled platelets. The antithrombotic effects of TFPI were studied after soaking the AT plaques for 30 minutes in a solution containing r-TFPI (5 mg/mL) and compared to similar plaques soaked in buffer (placebo).

Results: As we have previously reported, lipid-rich atherosclerotic plaques are highly thrombogenic, as demonstrated by the heavy platelet deposition on them, $597 \pm 56 \times 10^6$ platelets/cm². When the AT plaques were treated with r-TFPI ($n = 31$), they showed reduced thrombogenicity ($179 \pm 12 \times 10^6$ platelets/cm²; $p < 0.001$) as compared with the buffer-treated plaques ($n = 29$).

Conclusions: Inhibition of TF by r-TFPI significantly reduces the

thrombogenicity of the lipid-rich human atheromatous plaques at flow conditions encountered in mildly stenosed coronary arteries. Our data suggest that the specific inhibition of TF by TFPI may offer a new therapeutic approach to reduce the thrombotic complications associated with spontaneous or angioplasty-induced rupture of AT plaques.

C7. Use of the FemoStop System as an Alternative to Surgical Repair of Femoral Artery Pseudoaneurysm. Roxana Mehran, George Dangas, John A. Venditto, Samin K. Sharma, Srinivas Duvvuri, Thomas Cocke, Jonathan D. Marmur, John A. Ambrose. Cardiovascular Institute, Mount Sinai Medical Center, New York, NY.

Statement of the Problem: Local pseudoaneurysm formation is a well-documented complication of femoral artery puncture in patients undergoing percutaneous interventional procedures. Surgical repair is the standard treatment option in most cases. Recently there has been success in obliterating these pseudoaneurysms by ultrasound-guided short-term compression. However, success with this method may be limited by the size of the pseudoaneurysm (generally less than 3.0 cm).

Methods: We retrospectively analyzed the use of prolonged femoral compression using a FemoStop system (USCI) in seven patients (ages 62–84 yrs.) who developed pseudoaneurysm of the femoral artery following an interventional procedure (between 2/94 and 8/94). In all patients, pseudoaneurysm was initially diagnosed clinically and then confirmed by ultrasound. All of them subsequently had unsuccessful ultrasound-guided pseudoaneurysm compression.

Results: The size of the pseudoaneurysm ranged from 2.8 cm to 4.0 cm in diameter (mean 3.2 cm). All patients had the FemoStop system placed over the pseudoaneurysm with continuous pressure of approximately 20 mmHg below systolic pressure for 12 to 18 hours. Six of seven patients (86%) had successful obliteration of the pseudoaneurysm confirmed by ultrasound without need for surgical repair. The only complication of the procedure was skin abrasion in two of seven patients (28%).

Conclusions: Our results suggest the use of the FemoStop system to obliterate pseudoaneurysms of the femoral artery as an alternative to surgical repair. These preliminary results need to be confirmed in a larger prospective trial to determine the acute and chronic benefit and cost-effectiveness of this non-invasive treatment of femoral artery pseudoaneurysms compared to ultrasound guided compression followed by surgical repair when unsuccessful.

C8. The Effects of Long-Term Nifedipine GITS vs. Verapamil SR Antihypertensive Therapy on Coronary Physiology. J. Diamond, J. Machac, M. Henzlova, A. Gharavi, A. Travis, R. Phillips. Cardiovascular Institute, Mount Sinai Medical Center, New York, NY.

Statement of the Problem: The effects of long-term antihypertensive treatment with calcium channel blockers on coronary physiology are not well characterized.

Methods: We examined 22 patients (13M, 9F; diastolic BP ≥ 100 mm Hg after two weeks on placebo) randomized to either nifedipine GITS or verapamil SR. The extent of BP reduction, LV mass regression, change in coronary flow reserve (CFR), and coronary resistance reserve (CRR) were measured at baseline (base.), and after 6 months treatment (Rx). LV mass was measured by echocardiography. CFR & CRR were quantified by split-dose thallium-201 perfusion imaging. The ratio of anterior, septal, inferior, and lateral segment counts during coronary vasodilatation by intravenous adenosine (170 mcg/kg/min), divided by baseline counts, defined CFR. CRR = stress mean arterial pressure/(rest mean arterial pressure $\times$ CFR ratio).

Results: Results were as follows:

	All subjects
base. office BP mmHg	173 $\pm$ 16/111 $\pm$ 9
base.-Rx office BP	-27 $\pm$ 18/-18 $\pm$ 11*
base. LV mass†	109 $\pm$ 25
base.-Rx LV mass	-15 $\pm$ 18*

Verapamil SR		Nifedipine GITS	
180 $\pm$ 16/113 $\pm$ 10		166 $\pm$ 12/110 $\pm$ 7	
-29 $\pm$ 21/-21 $\pm$ 13*		-24 $\pm$ 15/-16 $\pm$ 9*	
110 $\pm$ 29		107 $\pm$ 21	
-14 $\pm$ 21*		-16 $\pm$ 16*	
base. CFR&CRR‡	1.5 $\pm$ 0.3	0.6 $\pm$ 0.09	
base.-Rx CFR&CRR	0.0 $\pm$ 0.2	0.0 $\pm$ 0.09	
1.5 $\pm$ 0.2	0.6 $\pm$ 0.1	1.6 $\pm$ 0.03	0.6 $\pm$ 0.07
0.09 $\pm$ 0.19	0.0 $\pm$ 0.01	-0.05 $\pm$ 0.2	0.0 $\pm$ 0.08

* $P < 0.05$.

† LV mass (gm/m² by PENN convention) = 1.04[(IVS + LVID + PWT)³ - (LVID)³] - 13.6.

‡anterior segment (representative of other segments).

Conclusions: Despite significant BP reduction and LV mass regression over 6 months, there was no significant change in CFR or CRR in any myocardial segment for either drug group. This may in part contribute to the lower than expected reduction in coronary events observed in treated hypertensive patients.

C10. Tissue-Factor Activity after Angioplasty of Porcine Coronary Arteries: A Biphasic Increase. Richard Gallo, John T. Fallon, Vincenzo Toschi, S. David Gertz, Adrian Padurean, Yale Nemerson, James H. Chesebro, Valentin Fuster, Juan J. Badimon. Cardiovascular Biology Research Laboratory, The Cardiovascular Institute, The Mount Sinai Hospital, New York, NY.

Statement of the Problem: Tissue factor (TF) is a membrane glycoprotein that activates the extrinsic coagulation pathway and may play a role in the thromboproliferative response after balloon injury. TF is not present in significant levels in normal porcine coronary artery intima or media. This study was designed to determine the time course and location of TF activity in coronary arteries after balloon angioplasty (BA).

Methods: Paraffin-embedded sections of 53 porcine coronary artery segments, excised at 0 hr, 1 hr, 6 hr, 1 d, 3 d, 1 wk, 2 wk, 3 wk, and 4 wk after BA (balloon:vessel ratio, 1.7:1), were stained for TF antigen (Ag) using a rabbit antihuman polyclonal antibody, and for TF activity (Ac) by a recently developed *in situ* assay based on the binding of Digoxigenin-labeled r-Factor VIIa. Adjacent sections were stained for smooth muscle cell alpha-actin and for macrophages using muramidase in addition to hematoxylin-eosin and trichrome stains.

Results: Our results indicate a biphasic increase in both TF Ag and Ac after BA. TF activity was present early and late after angioplasty. One hour after arterial injury, TF Ag and Ac were visible in the media adjacent to the site of injury and in mural thrombus. TF Ag and Ac in thrombus persisted at 6 and 24 hours, but was markedly less at 3 d and 1 wk. At 2, 3, and 4 wk, TF Ag and Ac was again prominent in hypercellular neointima and smooth muscle cells of the media. The adventitia was markedly positive at all time points. Macrophages appeared most numerous at 3 d and 1 wk, exhibiting prominent TF staining during this period.

Conclusions: These results suggest a biphasic expression of TF after BA. The early increase may contribute to acute thrombosis, while the later expression of TF by the smooth muscle cells of the media and the hypercellular neointima may contribute to prolonged thrombin generation.

C11. Deletion Polymorphism of the Angiotensin-Converting-Enzyme Gene Is Independently Associated with Left Ventricular Mass and Geometric Remodeling in Hypertensive Subjects. A. Gharavi, J. Diamond, J. Jhang, M. Lipkowitz, R. Phillips. Hypertension Section, Cardiovascular Institute, and Division of Nephrology, Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: An insertion/deletion (I/D) polymorphism of the angiotensin-converting-enzyme (ACE) gene is associated with myo-

cardiac infarction, cardiomyopathy, and left ventricular hypertrophy. Left ventricular mass and geometry (degree of concentricity) are related to cardiovascular morbidity and mortality. The aim of this study was to evaluate the relationship between insertion/deletion polymorphism of the angiotensin-converting-enzyme gene and echocardiographic findings in a hypertensive population.

Methods: 2-D directed M-mode echocardiograms and 24-hour ambulatory blood pressure monitoring were performed in 64 hypertensive subjects. Echocardiographic measurements were assessed in blinding fashion using the Penn and ASE conventions. Left ventricular mass index and relative wall thickness were calculated. ACE genotypes were determined by polymerase chain reaction amplification of DNA prepared from leukocytes, using primers that encompass the polymorphic segment.

Results: Systolic ambulatory blood pressure was higher in subjects with the II genotype. All other patient characteristics were similar in all genotype groups. ANCOVA revealed significantly higher left ventricular mass index in the DD and the ID compared to the II genotype. There were also significant differences in relative wall thickness between the DD and ID and between the DD and II genotypes. On multiple regression analysis, systolic ambulatory blood pressure, gender, body mass index, and the ACE genotype were each independently related to left ventricular mass index ($R^2 = 0.53$). Systolic ambulatory blood pressure, race, and ACE genotype were each independently related to relative wall thickness ($R^2 = 0.34$). The ACE genotype explained an additional 3% and 4% of the variations of left ventricular mass index and relative wall thickness respectively.

Conclusions: In our study population, the ACE genotype was an independent determinant of left ventricular mass index and relative wall thickness, parameters that have been associated with increased cardiovascular risk. Screening for the D allele may allow early identification of hypertensive subjects at risk for target organ damage and cardiovascular disease.

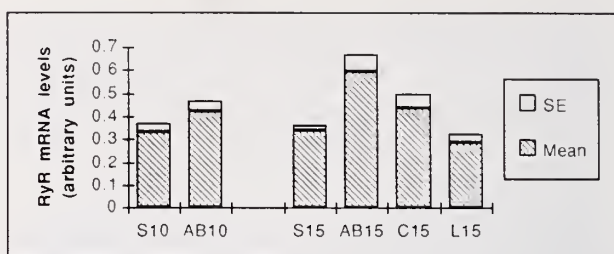
C12. Overexpression of Calcium Release Channel mRNA in Rats with Pressure-Overload Hypertrophy: Attenuation of Changes by Angiotensin Inhibition. L. O. Go, K. Dunskey, S. O. Marx, A. M. Cross*, R. T. Dowell*, A. R. Marks. Laboratory of Molecular and Cellular Cardiology, Dept. of Medicine, The Mount Sinai Hospital, New York, NY; *Division of Cardiology, Univ. of Kentucky, Lexington, KY.

Statement of the Problem: The ryanodine receptor (RyR) forms the major Ca^{2+} release channel in cardiac muscle activated during excitation-contraction coupling. We previously reported chamber-specific regulation of the RyR during end-stage human heart failure (J Clin Invest 1995;95(2):888-894). We sought to determine the time course of RyR regulation by studying the changes during pressure-overload hypertrophy in rats.

Methods: Adult male Sprague-Dawley rats were subjected to sham operation (S10, $n = 3$) or abdominal aortic banding for 10 weeks (AB10, $n = 3$); a second group of rats underwent sham operation (S15, $n = 3$) or aortic banding for 10 weeks followed by debanding and treatment for 5 weeks with saline (AB15, $n = 3$), captopril 100 mg/kg (C15, $n = 3$), or losartan 15 mg/kg (L15, $n = 3$).

Results: Echocardiographic assessment of LV wall thickness and fractional shortening in the animals before killing showed a trend toward increased wall thickness and decreased fractional shortening in AB10 compared to S10 rats, but the trend appeared to reverse after debanding. Northern blot analyses of total RNA isolated from each heart detected a single ~16 kb cardiac RyR mRNA. RyR mRNA levels were quantified using a phosphorimager and normalized to 28S ribosomal RNA levels (shown below).

Conclusions: We conclude that RyR expression is increased during the early phase of aortic banding before the onset of overt heart failure. This up-regulation progresses despite apparent resolution of LV echocardiographic changes after debanding, but appears to be attenuated by inhibition of the angiotensin system. These alterations of Ca^{2+} release channel expression may reflect the molecular mechanism underlying early hypertrophy and subcellular remodelling, processes which could be favorably affected by angiotensin inhibition.



C13. Interobserver Variability in Left Ventricular Measurements by Simultaneously Obtained Two-dimensional (2D) and M-Mode Echocardiography. J. S. Jhang, J. A. Diamond, R. A. Phillips. Hypertension Section, Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: Achieving low interobserver variability is a goal of echocardiographic-determined left ventricle (LV) mass measurements.

Methods: We evaluated interobserver variation using digitized, simultaneously obtained 2D and M-mode images of the LV. Sixty echocardiographic tracings from several ongoing hypertension trials were digitized on-line with an ATL Ultramark 6 scanner, coded, and read blindly in a random order by two independent observers using a commercially available digitizer (Nova MicroSonics). Cines of three consecutive frames of 2D and M-mode parasternal short axis views of the left ventricle were simultaneously displayed. Left ventricular dimensions from the M-mode were measured to determine LV mass. Interobserver measurements were correlated (Pearson correlation coefficient) and expressed as a percentage of the mean.

Results: The findings were as follows.

Measurement	Correlation†	% Difference
Interventricular septum	0.82*	10.0%
LV internal dimension	0.94	3.0%
Posterior wall thickness	0.75	10.2%
LV mass*	0.93	8.9%

* LV mass determined by the Penn convention protocol using the formula $LV\ Mass = 1.04[(IVS + LVID + PWT)^3 - (LVID)^3] - 13.6$.

† p values were all 0.0001.

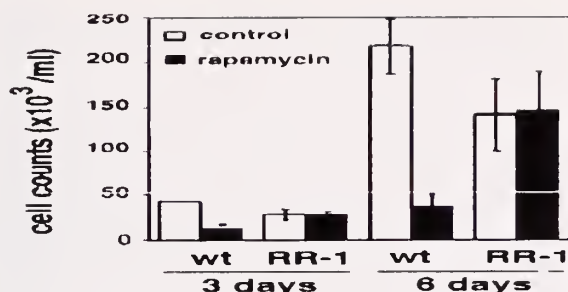
Conclusions: When read in a blinded fashion, interobserver variability (especially for LV mass) is small using digitized, simultaneously displayed cines of 2D and M-mode echocardiograms. This is likely due to the ability to discriminate myocardial wall edges (endocardium) from other associated structures such as tricuspid and mitral apparatus. This method may prove useful in studies of LV mass.

C14. Rapamycin Resistance in Myogenic Cells Is Associated with S6 Kinase-Independent Growth. Steven O. Marx, Thottala Jayaraman, David J. Harnick, and Andrew R. Marks. Laboratory for Molecular and Cellular Cardiology, Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: Recently, we reported that rapamycin (rapa) inhibits myogenic proliferation by causing G1/S cell cycle arrest.

Methods: To elucidate the mechanism, we developed rapa-resistant muscle cell lines (RR-BC3H1) by culturing in the presence of high concentrations of rapa.

Results: Rapa (<1 ng/mL) inhibits cell growth, ^3H thymidine incorporation, cell cycle kinase activation, and retinoblastoma protein (pRb) phosphorylation in wild type BC3H1 cells. Rapa (1-1000 ng/mL) had none of these effects in RR-BC3H1. The sequences of FKBP12 and part of the target of rapa (TOR2) homologue (in a region that confers rapa resistance in yeast) were shown to be wild type. In wild type cells, rapa-mediated inhibition of S6 kinase phosphorylation is thought to be critical for its antiproliferative action. RR-BC3H1 cells exhibited a fivefold higher S6 kinase protein level than wild type cells. However,



as in wild type cells, S6 kinase phosphorylation was inhibited by rapa in RR-BC3H1.

Conclusions: We have demonstrated S6 kinase-independent growth in RR-BC3H1; these cells proliferate, yet S6 kinase is inhibited in the presence of rapa. Thus, S6 kinase phosphorylation and activation does not play a critical role in cell cycle progression in these myogenic cells.

C15. Hemodynamic and Humoral Correlates of Insulin Resistance in Borderline Hypertensives. Robert A. Phillips, Lawrence R. Krakoff, Diane Finegood. Mount Sinai School of Medicine, New York, NY, and University of Alberta, Edmonton, Canada.

Statement of the Problem: The basis of the relation between insulin resistance and hypertension remains obscure. Common hemodynamic and humoral features might link these conditions.

Methods: To further understand the hemodynamic and humoral correlates of insulin resistance, 19 nonobese, glucose-tolerant untreated borderline or mildly hypertensive subjects were studied (body mass index [BMI] <27.8 kg/m², age 45 ± 9, mean ± SD). We examined the relation between insulin resistance (S_I), total catecholamines (CATS; norepinephrine & epinephrine), plasma renin activity (PRA), blood pressure (BP), and total peripheral vascular resistance (TPR). S_I (×10⁻⁴ min⁻¹(μU/mL) was determined from the frequently sampled intravenous glucose tolerance test using the minimal model method of Bergman. TPR (dynes·sec·cm⁻⁵) was calculated from cardiac output obtained from Doppler and 2-D echocardiographic (echo) examination of the heart and from BP at the time of the echo. PRA (ng/mL/hr) was determined from radioimmunoassay and CATS (pg/mL) from HPLC. 24 hour ambulatory BP monitoring (SBP and DBP, mm Hg) was obtained with a Spacelabs 90202 device.

Results: Ambulatory BP was 133 ± 9/85 ± 6 (SBP range 118–154, DBP range 77–100 mm Hg). S_I was 4.2 ± 2 (range 1.9–7.9). TPR was 2017 ± 474 (range 1101–3014). PRA was 0.84 ± 0.7 (range 0.10–2.6), and CATS were 280 ± 99 (range 128–513). BMI was 24 ± 2 (range 21–27.7). Insulin sensitivity (S_I) was inversely related to several variables at the *p* < 0.05 level: 24 hour DBP (*r* = -0.46); PRA (*r* = -0.54); CATS (*r* = -0.47); and TPR (*r* = -0.45, *p* = 0.05). In this nonobese population, S_I was not related to BMI or to age. In multivariate analysis that included CATS, PRA, and TPR, only PRA and TPR were independently related to insulin sensitivity.

Conclusions: Thus, insulin sensitivity (S_I) is related to hemodynamic and humoral parameters. The mechanism of these relations may include: (1) decreased insulin delivery in the setting of raised TPR; (2) raised TPR secondary to failure of insulin's vasodilator action; (3) compensatory increased PRA to generate angiotensin II, which at subpressor doses improves insulin sensitivity.

C16. Can Ease of Electrical Cardioversion Be Predicted by Transesophageal Echocardiographic Parameters of Left Atrial and Appendageal Size and Function? Frank Pollaro, David Vorchheimer, Lawrence Baruch, Stacey Rosen, Davendra Mehta, Edward Fisher, Noelle Langan, Anthony Gomes, Erdulfo DePeralta, Elena Pe, Jacqueline

Budd, Martin Goldman. Division of Cardiology, Bronx VA Medical Center and Mount Sinai Medical Center, New York, NY.

Statement of the Problem: Acute thromboembolic (TE) events following direct current electrical cardioversion (CV) for atrial fibrillation/atrial flutter are thought to be caused by "stunning" of the left atrium (LA) and left atrial appendage (LAA) during cardioversion. Although the mechanism of stunning is unknown, transesophageal echocardiographic (TEE) studies during CV show that serial shocks result in incremental reductions in LAA contractile function. The magnitude of stunning may conceivably be determined by the number of shocks needed to restore sinus rhythm (NSR). Thus, factors predicting need for multiple shocks may influence physician decisions to attempt CV. Historically, dilated and dysfunctional atrial have been considered resistant to CV.

Methods: We therefore analyzed successful electrical cardioversion in 51 patients with atrial fibrillation or atrial flutter to determine whether pre-CV TEE measurements of LA and LAA size and function would predict ease of cardioversion. CV protocol sequence was an initial shock: 50 or 100 Joules (J), with subsequent serial shocks of 200J, 300J, and 360J. Ease of cardioversion was defined as restoration of NSR following a single shock (SINGL) vs. multiple shocks (MULT). We measured total Joules delivered (JOUL), number of shocks (SH, mean), LA width M-mode (LA-M, cm), LA 2-dimensional area (LA-2D, cm²), LAA size (LAA, cm²), LAA peak emptying Doppler velocity (pk, cm/s), spontaneous echogenic contrast (SEC, graded 1–4+), left ventricular fractional shortening (FS, %), and number of thromboembolic events (TE) within 24 hours of cardioversion.

Results:

	n	JOUL	SH	LA-M	LA-2D
SINGL	29	93*	1.0*	4.8	23.8
MULT	22	457	2.5	4.7	27.6
LAA	LAApk	SEC	FS	TE	
5.4	41.7	1.5	27.1	2	
6.0	41.8	1.7	25.4	1	

* *p* = 0.0001, all others *p* = NS.

Conclusions: Patients requiring MULT shocks received a higher total energy and more shocks than those who cardioverted to NSR with SINGL shock. Patients requiring MULT vs. SINGL shock have similar LA and LAA mechanics, and thus the ease of restoring NSR during CV cannot be identified by echocardiographic parameters of LA and LAA size and function.

C19. A 29-Year-Old Moroccan Man with New Onset Right-Sided Weakness. Roxana Mehran, Lana Tsao, James H. Chesebro. Cardiovascular Institute, Mount Sinai Medical Center, New York, NY.

Case Report: A 29-year-old right (R) handed Moroccan man had a chief complaint of R sided weakness and difficulty with speech. He had a significant history of rheumatic heart disease with mitral stenosis and chronic arterial fibrillation (AF). He is s/p mitral valve (MV) repair and subsequent replacement with a mechanical prosthesis. He has a history of prior left (L) cerebrovascular accident with no residual weakness. Medications: coumadin, digoxin, lasix, and potassium. His last prothrombin time (PT) was 3 months prior to admission and was therapeutic. ROS is noncontributory.

Physical examination disclosed R sided facial droop, irregularly irregular heart rate at 90/min, JVD at 90 degrees, RV lift, normal mechanical clicks of prosthesis, loud P₂, II/VI holosystolic murmur at the LSB (increased with inspiration), no diastolic murmur, no gallops, clear lungs, a pulsatile liver, R sided motor weakness, and expressive aphasia. On admission, he had INR of 2.8, EKG: AF, R axis deviation, RVH, nonspecific ST changes. CXR: cardiomegaly, RVH. CT scan: L parietal lobe infarct, no hemorrhage.

Hospital course: pt was admitted and intravenous heparin was administered. Transesophageal echocardiogram (TEE) revealed normal MV prosthesis, severely dilated atria and ventricles, moderate to

severe RV and LV hypocontractility, severe TR, and a large L atrial thrombus. Pt was subsequently treated with coumadin and aspirin in addition to heparin.

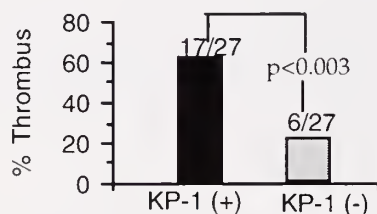
He was discharged taking coumadin and aspirin with INR of 4–5. Three weeks after discharge, repeated TEE revealed further enlargement of the L atrial thrombus despite therapeutic INR. Pt was then readmitted for in-hospital intravenous heparin therapy for two weeks and was subsequently discharged home on coumadin and subcutaneous heparin therapy. Repeat TEE showed no further enlargement of the thrombus and the patient is currently doing well at home without any further neurologic events.

C20. Inflammation and Thrombosis in Acute Coronary Syndromes: Insight from Directional Atherectomy Tissue Analysis. Billie Fyfe, Samin K. Sharma, George Dangas, Srinivas Duvvuri, Thomas Cocke, Jonathan D. Marmur, Roxana Mehran, John A. Ambrose. Cardiovascular Institute, Mount Sinai Medical Center, New York, NY.

Statement of the Problem: Thrombus (T) formation and acute plaque rupture are the major mechanisms in the pathogenesis of myocardial infarction (MI) and unstable angina (UA). Recent clinical studies have associated acute coronary syndromes and inflammatory process. The relationship between inflammation and T in UA has not been studied extensively. Analysis of tissue from directional coronary atherectomy specimens can be used to correlate inflammation and T.

Methods: We analyzed the results of immunohistochemical staining for macrophages (KP-1) in tissue from 54 culprit lesions: 19 with rest angina, 15 with new onset/crescendo, 10 post-MI, and 10 with stable angina. T was detected by H and E staining. KP-1 staining was graded as 0 to 2+, and 2+ was considered positive. Pathologic specimens were analyzed blindly.

Results: T was found predominantly in rest angina and post-MI. KP-1 staining was more common in all acute syndromes than in stable angina. KP-1+ was significantly associated with T, particularly in rest angina and post-MI where 14 of 17 KP-1+ lesions were T+.



Syndrome	T ⁺	KP-1 ⁺
Stable	0%*	20%†
New/Crescendo	20%	53%
Rest	63%**	58%‡
Post-MI	80%**	60%‡

** vs *, $p < 0.001$; † vs ‡, $p = 0.08$.

Conclusions: These data suggest a strong association between inflammation (KP-1+) and T in unstable angina at rest and post-MI.

C22. Clinical Variables Are the Best Predictors of Slow Flow during Rotational Atherectomy. Roxana Mehran, George Dangas, Alan Lotvin, Samin K. Sharma, Mahesh Kuthuru, Hari Kuncha, Srinivas Duvvuri, Thomas Cocke, Jonathan D. Marmur, John A. Ambrose. Cardiovascular Institute, Mount Sinai Medical Center, New York, NY.

Statement of the Problem: Rotational atherectomy (RA) is a new technique for percutaneous coronary revascularization. The Rotablator differentially ablates calcified atherosclerotic plaque, resulting in micro debris that dissolve in the blood stream distally. A major limitation of

RA is slow flow (SF) during ablation, defined as absent or slow distal runoff without obvious proximal pathology or distal filling defects of the epicardial vessels. This is related to embolization of atheromatous debris in the microvasculature.

Methods: To define the risk profile for SF, we evaluated clinical, angiographic, and procedural variables in 135 patients undergoing RA from 8/94 to 3/95. Patients were divided into two groups, SF and normal flow (NLF).

Results: SF occurred in 17 pts (12%). There was no difference between groups with respect to age, diabetes, smoking, hypertension, hypercholesterolemia, or stenotic lesions. Burr size and total ablation time were also similar.

Variable	SF	NLF	p
Female (%)	53	42	NS
β-blocker use (%)	65	31	.01
Rest angina (%)	53	28	.04
CP <48 hr RA (%)	17	8	.01
Post MI (%)	6	14	NS
MVD (%)	53	59	NS
LVEF (%)	54	53	NS
Ca ⁺⁺ (%)	71	67	NS
Length mm	21	24	NS
C lesion (%)	59	33	.04

LVEF, ejection fraction; CP < 48 hr RA, rest chest pain within 48 hrs of RA; MVD, multivessel disease.

Conclusions: Clinical variables like rest angina, CP < 48 hr RA, and β-blocker therapy were strong predictors of the development of SF. These data suggest that RA is a high risk in patients with unstable angina whose last episode of CP was within 48 hrs of RA, patients with rest angina, and patients undergoing β-blocker therapy.

C23. G-Protein Coupling of a Recombinant Inwardly Rectifying Potassium Channel. Marie-Noelle S. Langan, Kim W. Chan, Jin-liang Sui, Diomedes E. Logothetis. Division of Cardiology, The Mount Sinai Hospital, New York, NY.

Statement of the Problem: Adenosine and acetylcholine (ACh) stimulate cardiac potassium (K) channels via GTP-binding (G) proteins. Several G-protein-coupled inwardly rectifying channels have recently been cloned. We have isolated one such recombinant K channel (Kchan) from a human pancreatic cDNA library (where it was found to be most abundant). This channel showed 26 amino acid (aa) differences from a rat cardiac clone (rcKATP1/CIR) and only one aa difference from a channel referred to as a human cardiac KATP.

Methods: We have functionally expressed Kchan in *Xenopus* oocytes and recorded membrane currents using two electrode voltage and patch clamp methods.

Results: Hyperpolarizing pulses (to -80 mV) yielded measurable baseline current (1015 ± 294 nA; $n = 20$). BaCl₂ (200 μM) blocked a large component of the Kchan-generated current (707 ± 240 nA; $n = 20$). The current-voltage (I-V) relation of the barium-sensitive current with bath solutions of varying potassium concentrations showed inward rectification with reversal potentials as expected of a potassium selective channel. *Xenopus* oocytes coinjected with Kchan and hM2 receptor mRNA exhibited significant ACh-induced currents ($1.1 \mu A \pm 0.15$; $n = 19$) which were barium-sensitive. This agonist-dependent response was ablated by treatment with pertussis toxin ($n = 12$). The I-V relationship of the ACh-induced current revealed strong inwardly rectifying properties.

Conclusions: Single-channel recordings with and without ACh demonstrated very brief spiky openings (mean open time of 0.35 msec) and a small conductance (15–30 pS), which when compared to heterologous mammalian expression systems were similar to CIR but different from rcKATP.

C24. Delayed Surface Expression of Active Tissue Factor in Human Arterial Smooth Muscle Cells: A Potential Second Regulatory Mechanism. A. D. Schecter, J. T. Fallon, S. V. Thirukraman, O. Taby, C. L.

Rosenfield, M. Rossikhina, Y. Nemerson, M. B. Taubman. Divisions of Cardiology, Pathology, and Hematology, The Mount Sinai Hospital, New York, NY.

Statement of the Problem: Tissue factor (TF) is a 47kD transmembrane glycoprotein that initiates coagulation. TF is induced by growth factors in cultured rat aortic smooth muscle cells (SMC) and in the media and neointima of rat arteries after balloon injury. To investigate a potential role for TF induction in human arterial thrombosis, we have examined the regulation of TF in human aortic and coronary artery SMC. There was a greater than tenfold induction in TF mRNA levels 1–8 hours after treatment with growth agonists (serum, α -thrombin, PDGF BB and AA homodimers) by RNA blot analysis. Nuclear run-on assays and mRNA stability studies indicated that agonist-mediated accumulation of TF mRNA was due to enhanced transcription.

Methods: To study the cellular localization of active TF, human SMC were stimulated with growth agonists, fixed in 4% paraformaldehyde, and incubated with digoxigenin-labeled Factor VIIa. DigVIIa binding was detected with anti-digoxigenin antibody by light and confocal microscopy.

Results: Unstimulated SMC had minimal TF activity (i.e. VIIa binding). Active TF localized to the juxtanuclear region 4 after stimulation with growth agonists. At 16 hours, active TF was present in patches on the cell surface membrane. Similar patterns were seen using antibody against human TF. Treatment of VSMC with actinomycin D completely inhibited both the juxtanuclear accumulation and subsequent patches on the cell surface in response to PDGF; addition of colchicine at time zero prevented cell surface localization thus supporting the role for microtubules in the transit of TF to the plasma membrane.

Conclusions: TF mRNA and activity are highly regulated by growth agonists in human SMC. There is substantial delay in the transport of TF from the cytoplasm to the cell surface. Elucidation of the mechanism(s) underlying the transport and insertion of newly synthesized TF into the plasma membrane may provide novel approaches for regulating TF-mediated arterial thrombosis and coagulation.

C25. The Thrombogenicity of Human Atherosclerotic Plaque Components Is Predicted by Tissue Factor. Vincenzo Toschi, John T. Fallon, Richard Gallo, Maddalena Lettino, Antonio Fernandez-Ortiz, Lina Badimon, James H. Chesebro, Yale Nemerson, Valentin Fuster, Juan J. Badimon. Cardiovascular Institute, Mount Sinai Medical Center, New York, NY.

Statement of the Problem: Tissue factor (TF) is a membrane associated glycoprotein that initiates the activation of the extrinsic coagulation cascade by binding to factor VII/VIIa. TF antigen has been demonstrated in atherosclerotic plaques. We previously documented different thrombogenicity of various types of atherosclerotic lesions exposed to flowing blood in the Badimon perfusion chamber. In the present study we investigated the mechanism responsible for the different degree of thrombogenicity of plaque components.

Methods: Fifty human arterial segments, previously exposed to flowing blood, were stained for TF activity by a novel *in situ* assay based on the binding of digoxigenin-labeled r-Factor VIIa.

Results: Results of staining intensity and the amount of ^{111}In -platelet deposition on different exposed components are shown in the following table:

Substrate exposed (n)	Platelets/ $\text{cm}^2 \times 10^6$	TF staining score (0–3)
Lipid core (10)	712 ± 213	3 ± 0.1
Collagen matrix (9)	96 ± 16	1 ± 0.0
Foam cells (fatty streaks) (5)	97 ± 46	2 ± 0.01
Normal adventitia (6)	203 ± 58	2 ± 0.1
Normal tunica media (5)	134 ± 41	1 ± 0.0
Normal intima (15)	79 ± 16	1 ± 0.1

When all specimens are combined ($n = 50$), a strong positive correlation is found between TF activity and platelet deposition ($P < 0.01$).

Conclusions: Our data indicate that TF appears to be the major determinant of the prothrombotic activity of human atherosclerotic lesions.

C27. In Vivo Real-Time Monitoring of Thrombus Growth in Porcine Carotid Arteries with $^{99\text{m}}\text{Tc}$ -Platelets and ^{123}I -Fibrinogen. Richard Gallo, Adrian Padurean, Juan J. Badimon, Vincenzo Toschi, Maddalena Lettino, S. David Gertz, Shankar Vallabhajosula, Martin Lorenz, Wolfgang Eisert, Valentin Fuster, James H. Chesebro. Mount Sinai Medical Center, New York, NY.

Statement of the Problem: Current methods for detecting arterial thrombus are usually qualitative and thus limited to one or a few time points for monitoring thrombus growth and lysis. This study was designed to evaluate thrombus growth and evolution over time.

Methods: A recently developed miniature and implantable gamma spectrometry system (Karl Thomae GmbH, Germany) equipped with a 5×5 mm cadmium telluride radiation detector probe was used. Thrombus formation was monitored by minute-to-minute counting of $^{99\text{m}}\text{Tc}$ -platelets or ^{123}I -fibrinogen deposition over 2–4 hours in 20 porcine carotid arteries after different degrees of arterial crush injuries. Blood flow variations in the injured vessels were monitored by a Doppler flow meter. Sections of injured vessels were fixed, sectioned, and stained with H + E and trichrome.

Results: In the presence of extensive injury, such as exposition of the adventitia, the rise in slope of platelet deposition over time is steeper and is accompanied by a greater platelet deposition to the vessel wall. Lesser degrees of injury result in slower and lower levels of platelet deposition, exhibit greater fluctuations in counts concordant with flow variations (characteristic of embolization), and predicted mural thrombus formation. Total thrombus formation over time, as evaluated by the area under the platelet count curve, paralleled the degree of injury at histology. Final $^{99\text{m}}\text{Tc}$ -platelet counts at the site of injury prior to killing correlated highly with platelet counts determined by a traditional gamma well counter ($r = .93, p < .001$).

Conclusions: A new method for continuous real-time monitoring of platelet or fibrinogen deposition can quantitate the rate and amount of thrombus formation *in vivo*. This system will permit a more precise evaluation of antithrombotic agents on dynamic thrombus growth after arterial injury.

C29. The Effect of 100 Joules on Left Atrial Appendageal Stunning and Success of Cardioversion: A Transesophageal Echocardiographic Study. Lawrence Baruch, MD, Selvakumar Chockalingam, MD, Jonathan Taub, Eric Stern, MD, Patricia O'Dwyer, RDMS, Calvin Eng, MD. VA Medical Center, Bronx, New York.

Statement of the Problem: Electrical cardioversion of atrial arrhythmias is commonly performed. Echocardiography, both transthoracic and transesophageal (TEE), has assumed an increasingly prominent role in patients undergoing cardioversion of these arrhythmias. Echocardiography has identified markers for successful cardioversion, left atrial appendageal stunning after cardioversion, and thromboembolic events after cardioversion. The amount of energy required to electrically cardiovert a patient ranges from 50 to 360 Joules. The effect of the various energy levels on left atrial appendageal stunning and success of cardioversion has not been evaluated.

Methods: To determine the relationship between 100 Joules, left atrial appendageal stunning, and success of electrical cardioversion, we assessed left atrial appendage function as measured by peak emptying velocity (cm/sec), and increase in severity of smoke (SEC +), and return of sinus rhythm in patients undergoing TEE during and after a single 100-joule electrical shock during cardioversion of atrial fibrillation and flutter. We compared the group that was successfully converted to sinus rhythm (RSR) after 100 joules with the group that

remained with their atrial arrhythmia (AA) after a single 100-joule shock.

Results: Findings were as follows:

	n	pre	post	SEC +
RSR	15	55 ± 19	33 ± 19	33%
AA	10	36 ± 12.5	34.6 ± 10	0%
p			<.001	<.001

AA patients appear to have decreased LAA function when compared to RSR. In contrast to RSR patients, AA patients failed to demonstrate a significant decrease in LAA emptying velocity or an increase in smoke despite the delivery of an electrical shock. No patient developed new or increased smoke despite an electrical shock after unsuccessful cardioversion.

Conclusions: Thus, 100 Joules may be effective in cardioverting patients with preserved atrial function and cause stunning only in those patients who are successfully converted to sinus rhythm.

Endocrinology

E1. Cutaneous Microangiopathy in Diabetes Mellitus is Associated with Lipid Abnormalities, and is Further Impaired in Patients with Diabetic Foot Ulcers. Lisa G. Newman,* Chris Newton, Alex Stagnaro-Green.* New York, NY.

Statement of the Problem: Cutaneous microangiopathy may be important in the pathogenesis of diabetic foot ulcers (DU). Hypercholesterolemia has been associated with impaired microcirculation in various tissues. We determined the cutaneous microcirculatory flow (CMF) in patients with diabetes mellitus (DM), with and without DU. Associated factors, including lipid abnormalities, were evaluated to elucidate the pathogenesis.

Methods: Using laser doppler techniques, CMF was evaluated for foot pulp and dorsum (nutritive flow) of 25 healthy controls, 31 noninsulin-dependent DM, and 12 insulin-dependent DM. DU were present in 8 DM. Measurements were taken at 32°C and at 44°C to determine microcirculatory reserve. Patients had palpable pulses and no claudication. The presence of diabetic complications, proteinuria, and lipid profiles were determined.

Results: CMF was significantly lower ($p < 0.01$) at 44°C for both pulp (110 ± 55 vs 169 ± 75) and dorsum (33 ± 33 vs 51 ± 30), respectively, in DM versus healthy controls. The presence of DU in patients with DM was associated with lower dorsum CMF at 44°C (17 ± 8 vs 33 ± 33 , $p = 0.01$). For DM, dorsum CMF at 44°C was lower for DM with than for DM without lipid abnormalities. There was a direct relationship between CMF and HDL cholesterol ($p = 0.03$), and an inverse relationship between CMF and LDL/HDL ratios ($p = 0.03$) and LDL-cholesterol ($p = \text{NS}$).

Conclusions: (1) Cutaneous microangiopathy is present in DM and is associated with lipid abnormalities. Possible pathogenic mechanisms requiring investigation include subclinical arteriosclerosis and lipid-induced endothelial dysfunction. (2) CMF is further impaired in DU, and thus may be an important etiologic factor.

E12. Glucocorticoid-Induced Insulin Resistance: Dexamethasone Inhibits the Insulin-Stimulated Increase in Cell Surface GLUT4 Photolabeling in Rat Skeletal Muscle. S. Weinstein,* C. Wilson,† A. Pritsker,* and S. Cushman.† *Department of Medicine, The Mount Sinai School of Medicine, NY, and †Experimental Diabetes, Metabolism, and Nutrition Section, NIDDK, NIH, Bethesda, MD.

Statement of the Problem: The diabetogenic effect of glucocorticoid excess results in part from the development of peripheral insulin re-

sistance, wherein insulin fails to normally stimulate glucose uptake into skeletal muscle, the main site of insulin-mediated glucose disposal. We have recently found that glucocorticoid excess reduces insulin-stimulated, IGF-I-stimulated, and hypoxia-stimulated hexose uptake in rat skeletal muscle, and also reduces hexose uptake even in the absence of insulin, suggesting that glucocorticoids reduce muscle glucose transport, at least in part, by inhibiting the glucose transport system, per se.

Methods: To test the hypothesis that glucocorticoids reduce insulin-stimulated skeletal muscle glucose transport by inhibiting the recruitment of GLUT4 glucose transporters to the cell surface, we determined the effect of glucocorticoid treatment on cell surface GLUT4 using the impermeant glucose transporter photolabel, 2-N-(1-azido-2,2,2-trifluoroethyl)benzoyl-1,3-bis-(D-mannos-4-yloxy)-2-propylamine (ATB-BMPA), and GLUT4 immunoprecipitation. Male Sprague-Dawley rats were treated with dexamethasone (Dex) (0.9 mg/kg for 2 days) and compared to pair-fed controls. [^3H]-2-deoxyglucose ([^3H]-2-DG) uptake in isolated soleus muscles was measured under conditions in which uptake reflects glucose transport activity.

Results: In control muscles, [^3H]-2-DG uptake was stimulated eightfold by insulin (20 nmol/L). Dex treatment reduced maximal insulin-stimulated [^3H]-2-DG uptake by $48 \pm 4\%$ (mean $\pm$ SEM) and cell surface (ATB-[^3H]-BMPA-photolabeled) GLUT4 by $48 \pm 3\%$.

Conclusions: These experiments, which constitute the first use of this photolabeling technique in an insulin-resistant animal model, indicate that glucocorticoid-induced inhibition of insulin-stimulated glucose transport in muscle is due to reduced recruitment of GLUT4 to the cell surface, and that glucocorticoids do not alter the intrinsic functional capacity of cell surface skeletal muscle GLUT4 glucose transporters.

E13. An Immunocytochemical Study of the Influence of Conspecific Males on the GnRH Neuronal System in Normal and Hypogonadal Female Mice with Preoptic Area Grafts (HPG/POA). G. V. Rajendren and M. J. Gibson. Division of Endocrinology and Metabolism, Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: Immunocytochemical detection of Fos protein in GnRH neurons of normal and HPG/POA female mice was employed to assess GnRH neuronal activation following exposure to conspecific male stimuli.

Methods: Normal ovariectomized (OVX) mice were primed with estrogen (E) 48 h prior to testing, and subjected to either 2 h mating or 2 h exposure to male-soiled bedding or clean bedding. Mice were treated with or without progesterone (P) 4–5 h before testing.

Results: Robust induction of Fos immunoreactivity was observed in the GnRH neurons following mating in E + P-primed mice; several GnRH neurons in the E-primed females exposed to male-soiled bedding were also Fos+. None of the other treatment groups exhibited Fos immunoreactivity in their GnRH neurons. Plasma LH levels were also elevated in the E + P-primed females subjected to mating and in the E-primed females exposed to male-soiled bedding.

In continuing analyses of Fos immunoreactivity in GnRH cells within grafts in HPG/POA mice, we included several mice which failed to exhibit ovarian development after receiving grafts. Since normal OVX E + P-primed females consistently exhibited Fos immunoreactivity in their GnRH neurons, the HPG/POA females were OVX, primed with E + P and subjected to 2 h mating. In one HPG/POA, whose graft was in the lateral ventricle, there was no Fos immunoreactivity in GnRH neurons. In contrast, many GnRH neurons were Fos+ in the graft of another undeveloped HPG/POA after mating. Most of the graft tissue was located above the anterior commissure, a portion of it extending into the third ventricle. Neither of these females had GnRH innervation of the median eminence or elevated LH release.

Conclusions: Thus, even when POA grafts are not successful in stimulating ovarian development in HPG females, appropriate neuronal connections for activation of mating-induced Fos expression may be present. The identity of such afferents is under study.

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E14. Analysis of Human Pituitary Tumors for Tumor Viral DNA Sequences Using the Polymerase Chain Reaction. Michael Woloschak, Aiqin Yu, and *Kalmon D. Post. Departments of Medicine and *Neurosurgery, Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: Tumor viruses are known to have a role in the pathogenesis of many types of benign and malignant human tumors. The possible roles of these viruses in the development of human pituitary tumors has not been investigated. The polymerase chain reaction was used to screen human pituitary tumors for human papillomaviral and polyomaviral DNA sequences.

Methods: Sets of consensus primers were used in these experiments, which are capable of amplifying human papillomavirus (HPV) types 16, 18, and 33 and polyomavirus BK, JC, and SV40.

Results: Amplification products were not detected using HPV consensus primers in 30 tumors examined. Of 30 tumors, 26 demonstrated an amplification product with polyomavirus primers that hybridized to SV40 and BK internal probes; the product was confirmed in one tumor to be SV40 by direct sequencing. Ten normal postmortem pituitary samples were then similarly examined with polyomavirus consensus primers; 8 of 10 normal samples demonstrated a similar amplification product, which also hybridized with SV40 and BK internal probes by Southern blotting. Polyomaviral DNA sequences in normal and tumor samples were not present at levels detectable by genomic Southern blotting and expressed viral protein (large T-antigen) could not be demonstrated in positive samples by Western blot analysis.

Conclusions: Our findings are in agreement with those of other groups that polyomaviral DNA sequences are detectable at low levels in certain normal tissues, and our studies serve as the first report of polyomaviral latency in human pituitary tissue. We are unable to establish a role of polyomaviruses in pituitary tumorigenesis in this analysis.

E15. Abundance and State of Phosphorylation of the Rb Gene Product in Human Pituitary Tumors. Michael Woloschak, Aiqin Yu, Jiaqi Xiao, and *Kalmon D. Post. Departments of Medicine and *Neurosurgery, Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: Targeted disruptions of the retinoblastoma (Rb) gene result in a high frequency of pituitary tumors in heterozygous mice. Although our group and others have previously reported that LOH at the RB locus is rare, these studies have not excluded small and more frequent Rb gene abnormalities undetectable by this technique leading to primary Rb inactivation.

Methods: As a more sensitive means of detecting primary Rb gene abnormalities, we have performed Western blot analysis of several human pituitary tumors to examine the levels of Rb protein and to detect possible truncated forms of the protein associated with Rb gene mutations. In addition, the antibody used in these experiments differentiates the hypophosphorylated (active) and phosphorylated (inactive) forms of the Rb protein, allowing an assessment of indirect mechanisms which might lead to Rb inactivation in these tumors. Protein was isolated from 24 adenomatous and 6 postmortem human pituitary tissues by standard methods. Equal amounts of these samples were then subjected to Western blot analysis using a primary monoclonal antibody (PMG3-245, Pharmingen). Blots were then stripped and incubated with a primary β -actin antibody to control for protein loading and integrity.

Results: In all tumors, Rb protein was detected at levels ranging from 1.4 to 3.9-fold greater than levels detected in normal postmortem pituitary. There was no evidence of truncated forms of the Rb protein, and only the hypophosphorylated form of the protein was detected in both normal and pituitary tumor specimens.

Conclusions: Our findings provide evidence that loss of Rb is probably not common in human pituitary tumors. Our detection of only the hypophosphorylated (active) form of the Rb protein also argues against indirect mechanisms leading to Rb inactivation in these tumors. Although the predominance of the hypophosphorylated form of Rb in these tumors most likely reflects their low proliferative state, by this

analysis we cannot exclude the possibility of Rb mutations at phosphorylation sites or elsewhere in these tumors.

E16. Production of Soluble Prokaryotic Human TSH Receptor Extracellular Domain by Disulfide Bond Formation in the Cytoplasm of *Escherichia coli*. Y. Bobovnikova and V. Nguyen. Division of Endocrinology and Metabolism, Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: The reducing potential of *E. coli* cytoplasm prevents the formation of protein disulfide bonds, in contrast to the periplasmic compartment, which allows such bonds to be formed. Recently, *E. coli* mutants of the thioredoxin reductase (trx) gene were identified which allowed disulfide bonds to form in the cytoplasm (Derman et al., Science, 1993). We have taken advantage of this system to increase the yield of soluble human thyrotropin receptor extracellular domain (hTSHR-ecd).

Methods: hTSHR-ecd cDNA (amino acids 21-414) was inserted into the vector pGEX-2TK by directional cloning and used to transform the trx mutant *E. coli* AD494. Expression of hTSH-ecd was induced with IPTG, and cell sonicates were fractionated into insoluble and soluble fractions. The expressed hTSHR-ecd fusion protein was detected by Western blot analysis using a murine MAb directed against hTSHR amino acids 21-35.

Results: Similar amounts of hTSHR-ecd protein were present in the soluble and insoluble fractions. This result is in strong contrast to our own and other previously published reports of studies using other *E. coli* expression systems, in which most of the expressed hTSHR-ecd was in the insoluble fraction. In addition, analysis using reducing and nonreducing PAGE/SDS systems showed that most of the soluble hTSHR-ecd migrated as a refolded, disulfide bond-stabilized tetrameric species. The insoluble material migrated as unfolded monomers.

Conclusions: This new expression system offers unique advantages for future studies of structure and function of the receptor, as well as the binding of autoantibodies in autoimmune thyroid disease.

E17. Elimination of Unnecessary Thyroid Testing in the Clinical Laboratory. Edward J. Diamond, Terry F. Davies, Erlinda Concepcion, Michael R. Zimmerman. Division of Endocrinology and Metabolism and Center For Clinical Laboratories, Mount Sinai Medical Center, New York, N.Y.

Statement of the Problem: The clinical literature shows that most patients with hyperthyroidism or thyroid failure have abnormal concentrations of thyroid-stimulating hormone (TSH). It is unnecessary in most clinical situations to carry out a panel of tests to determine patient thyroid status. The goal of this study was to eliminate some of this inappropriate testing.

Methods: For the past two years we monitored requests for routine thyroid function tests (T4, TBG, TSH, and T3).

Results: We found that 47% of the requests were for all four analytes on single specimens. These findings led to the establishment of new criteria for thyroid function testing and the design of a new requisition form to facilitate our approach. The laboratory performs a third-generation TSH that (sensitive to 0.01 uIU/ML as a first-line thyroid function test. If the TSH is within the normal range (0.2-5.0 uIU/ML), no further tests are performed unless a reason is specified on the requisition form. An abnormal TSH elicits reflex testing—a T3 when the TSH is low, and a T4/TBG ratio when it is elevated, leading to a diagnosis of either thyrotoxicosis or thyroid hypofunction.

Conclusions: Since starting this strategy 10 months ago, we have eliminated over 3700 tests (>4500/year). This constitutes 26% of the requests for T4, T3, and TBG tests and obviously decreases hospital costs. In addition, users are becoming educated to this approach; they are ordering fewer tests and submitting more requests that are limited to the TSH test.

E19. Clonal T-Cell Response to hTSHR Peptide Revealed by Radio-Labelled PCR. Munetoshi Nakashima, Andreas Martin, and Terry F. Davies. Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: Peripheral blood mononuclear cells (PBMC) from a patient with Graves' disease with extrathyroidal manifestations (including pretibial myxedema and acropachy) were stimulated with a panel of 29 overlapping, synthetic peptides of the extracellular domain of the human TSH-receptor (hTSHR; J. Morris, Mayo Clinic) and showed a significant proliferative T-cell response toward peptide 121–140 (stimulation index, 5.3; *t*-test, $p < 0.05$).

Methods: To evaluate the clonality of the responding T cells, uncloned T cells from one-week cultures of PBMC with peptide 121–140 and control peptide were compared for their human T-cell receptor (hTcR) V gene families using a radio-labeled PCR approach and confirmatory sequencing. The radio-labeled PCR is based on the differing lengths of the hTcR complementarity-determining region 3 (CDR3), which is subject to random nucleotide additions and deletions. Hence T-cell clones can have CDR3 regions of different lengths which can be visualized as distinct bands for each hTcR V gene family. The radio-labeled PCRs were performed with 18 V α and 21 V β oligonucleotides as forward primers and a ³²P-labelled C region oligonucleotide as reverse primer. PCR products were then separated on polyacrylamide gels and exposed.

Results: Enhanced bands were observed only in the cultures of peptide 121–140 stimulated T-cell cultures compared to controls. These bands were seen in a limited set of V gene families (V α 14, V α 15, V β 1 and V β 7). Clonality was confirmed by sequencing the cloned V β hTcR PCR-ligation products of V β 1 and V β 7 (four bacterial colonies per V gene family). Three out of 4 sequences for V β 7 (75%) showed complete identity of their CDR3 regions (6 amino acids) and their J segments (J β 2.1), whereas 4 sequences obtained for the V β 1 family were heterogeneous for both CDR3 and J segments.

Conclusions: Radio-labeled PCR is a practical approach for the rapid identification of peptide-induced, expanded T cells. Our data suggest that the T-cell autoimmune response to thyroid peptide is restricted but involves both clonal and nonclonal elements.

E20. GnRH Axonal Outgrowth from the Preoptic Area (POA) to the Mediobasal Hypothalamus (MBH) in Organotypic Cultures: A Time Course Study. M-C. Rogers, A-J. Silverman,¹ M. J. Gibson. Division of Endocrinology and Metabolism and Fishberg Center for Neurobiology, Mount Sinai School of Medicine, and ¹Dept. of Cell Biology and Anatomy, Columbia University, New York, NY.

Statement of the Problem: GnRH terminals project in vivo to the median eminence of the MBH along a stereotypic route. When hypogonadal mice receive an embryonic POA graft in the third ventricle, GnRH outgrowth to the median eminence may be seen as early as five days after implantation.

Methods: In our organotypic culture system, tissue was placed inside an insert chamber on a porous membrane coated with collagen and laminin, and fed by capillarity from the underlying defined media. In earlier studies, we noted that when E15 POA was cultured with MBH and processed for GnRH immunoreactivity 7 days later, significantly greater GnRH axonal outgrowth was observed on the side of the POA directly facing the MBH co-explant than on the side away from the MBH ($p < 0.0001$). Such differential outgrowth was absent with control co-explants (Endo Soc Abst 1995). These results suggested the presence of an MBH-derived chemotropic diffusible substance attractive for GnRH axons.

Results: In the present study, when explants were cultured from one to 10 days, we documented increased GnRH axonal outgrowth from the POA over time. At one day of culture the number of GnRH fibers was too low to detect significant preferential outgrowth. However, the number of GnRH fibers was significantly higher on the side facing the MBH after 4, 7, and 10 days of culture ($p < 0.01$). In addition to being more numerous after 10 days of culture, GnRH fibers appeared longer, often entering the MBH explant. GnRH cell number decreased by

13.9% between 1 and 4 days of culture, by 18.2% between 4 and 7 days, and remained stable thereafter.

Conclusions: Preferential GnRH outgrowth to the MBH was observed throughout the time course, indicating that the MBH chemotropic action was maintained as long as 10 days in culture. We have observed unidentified cells and processes on the membrane between the co-explants. Further experiments are under way to distinguish potential chemotropism from the possible role of such cellular elements.

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E21. T-Cell-Receptor V Gene Selection in Human Thyroid Organoids. J. Zhang, N. Matsuoka, M. Nakashima, T. F. Davies, P. Unger,* L. D. Shultz,† and A. Martin. Departments of Medicine and Pathology,* Mount Sinai School of Medicine, New York, NY, and The Jackson Laboratory,† Bar Harbor, ME.

Statement of the Problem: We have used a human thyroid organoid model in the *scid* mouse to examine the interaction of T cells and their thyroid targets cells in an in vivo environment.

Methods: Campath-1 monoclonal antibody was used to remove lymphocytes from human thyroid monolayer cells by complement-mediated lysis, and the resulting thyrocytes were resuspended in a basement membrane gel and transplanted into *scid* mice, where they reorganized into thyroid neofollicles. To study the long-term effect of thyrocytes on the human peripheral T-cell repertoire, Graves' disease thyrocytes were Campath-1-treated and mixed with autologous peripheral blood mononuclear cells (PBMC) prior to organoid construction and transplanted s.c. into *scid* mice (2×10^6 thyrocytes and 3×10^6 PBMC/organoid). Five weeks later, organoids were explanted, total cellular RNA extracted and analyzed for human T-cell receptor (hTcR) mRNA using primers for the hTcR constant region (C β 2) as well as hTcR variable (18 V α and 20 V β) gene families.

Results: In comparison to peripheral blood and control organoid (PBMC/fibroblasts), where most hTcR V genes were expressed, there was a marked reduction in the numbers of hTcR V α and hTcR V β families in PBMC/thyrocyte organoids (mean number of both V α and V β families in PBMC/thyrocyte organoids, 7.0 ± 2.2). Organoids constructed with Campath-1-treated thyrocytes alone contained no detectable hTcR transcripts. Among both hTcR V α and V β families, certain hTcR V genes were predominant: V α 1 ($42 \pm 15\%$), V β 4 ($19 \pm 8\%$), and V β 5 ($29 \pm 9\%$) differed significantly from other hTcR V gene families ($p < 0.01$, ANOVA, Tukey's protected *t*-test).

Conclusions: Both V α 1 and V β 5 were consistently present in 5/5 mixed cell organoids and were also present in the original thyrocytes, suggesting intraorganoid selection for certain hTcR gene families from the peripheral repertoire. This model permits the reconstruction of hTcR V gene selective events in an in vivo environment and offers a potential window on the early stages of human autoimmune pathogenesis.

Gastroenterology

G11. Superficial Crohn's Colitis: A Study of Eight Cases. J. George, G. M. Groisman, and N. Harpaz. Departments of Pathology and Medicine (Div. of Gastroenterology), The Mount Sinai Medical Center, New York, NY.

Statement of the Problem: Transmural chronic inflammation is regarded as a hallmark of Crohn's disease and a major diagnostic criterion distinguishing Crohn's colitis (CC) from ulcerative colitis (UC). However, there exists a subset of patients with a form of CC that is

predominantly mucosal rather than transmural, i.e., superficial Crohn's colitis (SCC).

Methods: To characterize this condition, we reviewed the histologic slides and clinical records of a series of patients who had undergone colectomy for IBD, most between 1991–4, and whose colons had demonstrated (1) typical gross appearances of UC, (2) absence of transmural inflammation, or transmural inflammation limited to <5% of the inflamed colon, but (3) diagnostic features of CC.

Results: Eight colectomies (3 total, 5 subtotal) were identified, 7 with pancolitis and one with continuous colitis commencing at the hepatic flexure. Two specimens included ileal segments with obvious gross characteristics of Crohn's ileitis. Microscopically, the colitis in 5 cases was limited exclusively to the mucosa and submucosa. The histology in 4 of these cases was nonspecific and indistinguishable from UC, except that 3 contained small numbers of typical Crohn's granulomas in the mucosa and 1 showed both submucosal neural hypertrophy and anal fistulae. One case was histologically distinctive, showing numerous mucosal granulomas and preservation of goblet cells. Three of the 8 specimens contained one or two microscopic foci of transmural inflammation with typical Crohn's histology including granulomas, but elsewhere the histology was indistinguishable from UC. The preoperative diagnosis was CD in 3 cases and UC in 5. The diagnoses of CD were based on fistulae (ileal, perianal, and rectovaginal); one case was also identified pathologically based on granulomas in biopsies. Two of these 3 cases developed recurrences. Three of the 5 patients diagnosed preoperatively as UC underwent one stage protocolectomies and construction of ileoanal reservoirs, of whom 2 subsequently developed refractory granulomatous pouchitis requiring pouch resection. Four of the 8 patients remain free of recurrences after an average 25-m follow-up (range, 3–39 m).

Conclusions: SCC is likely to be misdiagnosed as UC clinically and pathologically, although it seems to be prognostically similar to ordinary CC. Correct diagnosis depends on adequate sampling of colectomy specimens and regard for the diagnostic significance of clinical and pathologic stigmata of CD, such as ileitis, fistulae, granulomas, and unexplained transmural inflammation, even if they occur focally in specimens that are otherwise characteristic of UC. SCC may account for some cases of Crohn's disease and refractory pouchitis developing in patients thought to have UC.

GI2. Rarity of Fistulae in Crohn's Disease of the Jejunum. J. F. Marion, P. Lachman, A. J. Greenstein, D. B. Sachar. Division of Gastroenterology and Department of Surgery, Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: We compared the fistulizing tendency of Crohn's disease involving the jejunum versus ileum.

Methods: We reviewed the records of 1,920 patients with Crohn's disease admitted to The Mount Sinai Hospital between 1960 and 1994.

Results: Fifty-eight of the 1,920 cases (3%) had jejunal involvement. Of these 58 patients, 6 (10%) had fistulae originating from the jejunum. Four of the cases of jejunal fistulae emerged from a subgroup of 41 patients who had both jejunum and distal ileum involvement (9.8%); by contrast, there were 12 cases of ileal fistulae arising from the same subgroup (29%, $p = 0.05$). As another measure of the relative rarity of jejunal versus ileal fistulization, there were 252 cases of ileal fistulae among 723 patients in our overall series with distal ileal Crohn's disease (34%), compared to the 10% (6/60) frequency of jejunal fistulization ($p = 0.001$). Only 50% (3/6) of our cases of jejunal fistulization were spontaneous, compared to 86% of a random sample (43/50) from our 252 cases of fistulae with ileitis. The development of jejunal fistulae did not appear to depend on the presence of stricturing, being nearly as common among nonstricturing cases (2/27, 7.4%) as among stricturing cases (4/31, 13%; $p = \text{NS}$).

Conclusions: The inherent proclivity of Crohn's disease to fistulize thus appears to increase with progressively distal location in the gastrointestinal tract. Perhaps bacterial flora are among the several putative factors that promote fistulization in Crohn's disease.

GI4. The Utility of Empirical Therapy for *Helicobacter pylori* (HP) in a Population with High Prevalence of Infection. M. E. Hirth, S.

Mumtaz, S. Setaruddin, Y. Twersky. Department of Medicine, Division of Gastroenterology, Mount Sinai Services at Queens Hospital Center—Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: The prevalence of HP in population with low socioeconomic status is similar to the high rate found in underdeveloped countries where most adults are infected. In the setting in which the symptoms are suggestive of peptic ulcer disease (PUD), a short course of empirical therapy may be indicated prior to more extensive evaluation such as endoscopy. The aim of this study was to evaluate the frequency of HP infection in patients who underwent endoscopy in a municipal hospital in New York City and to estimate the frequency with which empirical therapy for HP would have been an appropriate choice.

Methods: A total of 153 patients who underwent diagnostic endoscopy were studied. They were divided into two groups based on whether symptoms attributable to PUD were present or absent. The symptomatic group included patients with complaints such as abdominal pain, hematemesis, and dyspepsia who failed an empirical trial of H₂ blockers. The second group included patients with endoscopy as evaluation for anemia or occult GI bleeding who were asymptomatic. All patients had one or more antral biopsies submitted to pathology assessment and evaluated for the presence of HP by Giemsa stains.

Results: In the symptomatic group of 141 patients, 105 (74%) were positive (+) for HP and 36 (26%) were negative (–). In the second group of 12 patients only 4/12 (33%) were positive. In the symptomatic group, who were HP+ the most common endoscopic finding was an ulcer. Either DU, GU, or both were seen in 49/105 (47%); gastritis occurred in 37/105 (35%). In the symptomatic group who were HP– the most common endoscopic finding was gastritis, which occurred in 12/36 (33%); DU, GU, or both were found in 9/36 (25%). In the symptomatic group, endoscopy results was abnormal in 128/141 (91%). The combination of normal results on endoscopy and negative HP were observed in only 7/141 (5%) of the patients.

Conclusions: In a patient population with high prevalence of HP who had symptoms attributable to PUD, the frequency of HP infection was high (74%) and significant endoscopic findings were detected in a majority (91%). Normal endoscopy results and absence of HP occurred in only a small fraction (5%) of the symptomatic patients; it would therefore have been correct to treat the vast majority of them. As non-invasive tests such as HP breath tests become commercially available, further studies may be needed on the utility of empirical treatment in a selected group of patients with a high prevalence rate of HP.

General Medicine

GM1. Pulmonary Embolism (PE) in Different Ethnic Populations. M. Chow, M.D. Internal Medicine, Mount Sinai Services at Elmhurst Hospital, NY.

Statement of the Problem: Previous studies (Chau KY, Yuen ST, Ng THK, Ng WF. An autopsy study of pulmonary thromboembolism in Hong Kong Chinese. *Path* 1991; 23:181; Tinckler LF. Absence of pulmonary embolism in Asia? *Br Med J* 1964; Feb 22:502.) suggested a relatively low incidence of PE in southeast Asian populations.

Methods: All cases of PE over a 16-month period in a municipal hospital in New York City were reviewed. Patients were mostly immigrants from different parts of the world, a significant portion from southeast Asia. A matched-pair case control study was done. Cases of PE were identified from (1) postmortem study, (2) all high-probability ventilation-perfusion results scan (pulmonary angiogram was not available), (3) discharge diagnoses. Subjects were defined as patients whose ethnic origin was southeast Asia (China, Hong Kong, Korea, Philippines, Vietnam, etc.). Controls consisted of the first patient ad-

mitted to the same service on the same day with the same sex and within the same age range. Subject cases of PE numbered 42, and 38 controls were identified. Thus, only 38 matched pairs were entered for odds ratio calculation.

Results: The matched-pair odds ratio is 20%.

Conclusions: This study shows that PE is less common in south-east Asia than elsewhere. Further study should be done to confirm this finding and delineate the causes.

GM2. Evaluation of LVEF by QRS Complex Analysis. S. Sen, M. Cargom, M. Schori. Englewood Hospital and Medical Center, Englewood, NJ.

Statement of the Problem: Left ventricular ejection fraction (LVEF) can be inexpensively estimated by analysis of ECG. The aim of this study was to compare LVEF determined by QRS analysis with measurements obtained from MUGA scanning.

Methods: LVEF was assessed retrospectively in 30 patients admitted to Englewood Hospital and Medical Center with AMI. Serial 12-lead surface ECGs were scored by a 29-point system based on the duration of the Q and R waves and on the ratios of R to Q and R to S amplitudes. After scoring, LVEF was calculated by the equation:

$$\text{LVEF (\%)} = 60 - (3 \times \text{QRS score})$$

Inclusion criteria were an MI documented by cardiac enzymes and LVEF estimated by MUGA scanning. The presence of LVH, RUH, RBB, posterior wall MI, and concurrent VHD excluded subjects from the study.

Results: Ages ranged from 44 to 72 years; sex distribution was 22 M/8 F. In 50% of the cases the MI was the first. With first MI, the lesion was localized in the anterior wall in 6, the anterolateral wall in 4, and the inferior wall in 5. Overall, in 73% of patients there was a good correlation between the calculated LVEF when compared to MUGA scanning. In 30% of patients, the calculated LVEF was overestimated by 10%–14%. Better correlation was found in patients with LVEF $\leq$ 40%. The scoring system equally estimated LVEF irrespective of the presence of more than one MI.

Conclusions: ECG analysis can provide important indirect quantitative information of LVEF after AMI. ECG is noninvasive, can easily be repeated, and is inexpensive, thus providing an easy tool to follow patients with noncomplicated MI or serving as a screening test for patients who will require MUGA scanning as high-risk patients prior to surgery. The QRS scoring system can be programmed in automated ECG machines, thus providing instant scoring.

GM3. Outcome of In-Patient CPR at Englewood Hospital and Medical Center: Favorable Outcome Predictors. M. Airood, Z. Iskandarani, M. AlSabbagh, and M. P. Schori. Englewood Hospital and Medical Center, Englewood, NJ.

Statement of the Problem: Nationwide, CPR outcome is predicted by age of patient, initial rhythm, and duration of code, with wide variation in outcome among different centers.

Methods: We conducted a retrospective chart review for in-hospital CACs over 9 months. Out-of-hospital CPR's (ER) were excluded. The relationship between a number of factors (age, admission diagnosis, co-morbid illness, patient disposition, duration of CPR code, initial rhythm, timing of code, code runner, and number of CPRs performed on each patient) and survival was evaluated to see whether any of these factors influenced survival.

Results: Initially, 25/97 (26%) patients survived; 15 died (2 within 24 hours after an initially successful CPR); 10 (11%) were discharged from hospital alive. Survival rate was 38% for patients with cardiac admission diagnosis, 21% for noncardiac admission diagnosis. Survival rate was 35% for patients with less than 2 co-morbid illnesses vs. 23% for those with 2 or more. The rate of survival on telemetry was 28%, vs. 29% in-unit and 22% on regular floor. The rate of survival on teaching

service was 28% vs. 20% on nonteaching service. Initial cardiac rhythm of asystole was associated with a survival rate of 17%, vs. 43% for ventricular fibrillation, 47% for ventricular tachycardia, and 27% for PEA and others. Codes $\leq$ 20 minutes duration had survival rate of 47% vs. 12% for codes $>$ 20 minutes duration. Codes conducted by attendings had 31% survival rate vs. 32% for fellows vs. 23% for senior residents. Patients who had one CPR code had a survival rate of 28%; for those who had 2 or more codes the rate was 18%.

Conclusions: Consistent with other studies, favorable CAC outcome predictors were age $<$ 70; admission diagnosis of cardiac disorder; $\leq$ 2 co-morbid illnesses; monitored setting; teaching service; initial rhythm other than asystole; and CPR code duration $<$ 20 minutes.

GM4. Infective Endocarditis at Englewood Hospital and Medical Center. E. Caceres, M. P. Schori, and S. Shafi. Englewood Hospital and Medical Center, Englewood, NJ.

Statement of the Problem: All cases of infective endocarditis at Englewood Hospital and Medical Center between December 1, 1991 and November 30, 1994 that were diagnosed as ICD 9 code 421.0 (acute and subacute bacterial endocarditis) and 421.9 (acute endocarditis unspecified) were reviewed for the present study.

Methods: Thirty-six cases were selected. The average age of the patients was 66 years old (range 22–95). Males slightly predominated over females (20 vs. 16). Fever (94.4%) and murmurs (83.3%) were the most common signs and symptoms. Embolization to the central nervous system was the most common complication. Fifty-two percent of the patients did not have any predisposing cardiac lesion. Seven patients (19.4%) had dental work performed prior to the diagnosis of endocarditis. Six had a known history of valvular disease (no information was available on the use of antibiotic prophylaxis). The infective organism was isolated in 97.2% of the cases. *S. viridans* and *S. aureus* were the most prevalent organisms (38.8% and 36.1% respectively). One culture was negative. All patients with history of intravenous drug abuse had cultures positive for *S. aureus*. Transthoracic and transesophageal echocardiograms identified vegetations in 55.5% of the cases. The most common affected valve was the mitral (35.9%), followed by the aortic (20.5%), tricuspid (5.1%), and pulmonary (2.6%). No valvular lesion was found in 35.9% of the patients. In most of the cases the diagnosis was suspected on the basis of positive blood culture and physical findings.

Conclusions: Information obtained through this study is a reflection of the data available in the literature. The initial treatment was varied, except for cases in which blood cultures gave the initial clue to the presence of an intravascular infection.

GM5. A Comparison of Four Bowel-Care Modalities in Patients with Spinal Cord Injury. I. Amir, R. Sharma, W. A. Bauman, M. A. Korsten. Section of Gastroenterology, Spinal Cord Damage Research Center, Bronx Veterans Affairs Medical Center, Bronx, NY, and Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: Difficulty with evacuation is a major problem affecting the quality of life among patients with spinal cord injury. Bowel evacuation is generally accomplished by a combination of dietary fiber, digital stimulation, enema, suppositories, and stool softeners. However, it is not known which of these approaches is better than the others in providing good bowel evacuation. To compare the efficacy of four standard bowel-care preparations, we assessed colonic transit time (CTT) in seven hospitalized spinal cord injury patients in an open-labeled trial.

Methods: Seven male hospitalized patients were studied. The mean age of subjects was 45 y (range 22–76) and the mean interval since injury was 16 y (range 2–25 y). All patients had complete traumatic transection of spinal cord between the C-4 and T-11 vertebral levels. None of these patients had bowel problems prior to spinal cord injury. Each patient was assessed by a neurologist to accurately deter-

mine the level of injury. Each of seven subjects had four determinations of total and segmental colonic transit time after either bisacodyl suppositories, glycerine suppositories, mineral oil enema, or docusate sodium mini enema (Theravac SB), in addition to digital stimulation. After one week of each regimen, each subject ingested 20 radio-opaque markers on three successive days. On day 4, each subject had plain x-rays of the abdomen. Clonic transit time was calculated as previously published (Metcalf et al., *Gastroenterology* 1987;92:40–47). The data was analyzed and statistical comparisons were performed by ANOVA. Changes in bowel evacuation time and subjective assessment by using a DWE (difficulty with evacuation) score were also recorded.

Results: CTT was least with docusate sodium. Mean total CTT was 32.0 h with docusate sodium, 34.5 h with mineral oil enema, 47.6 h with bisacodyl suppositories, and 48 h with glycerin suppositories. There was no significant difference in CTT using docusate sodium or mineral oil enema (7.2 vs 12.6 h, $p > 0.05$), both of which produced significantly shorter results ($p < 0.05$) than bisacodyl (22.0 h) or glycerin suppositories (23.5 h). Docusate sodium also produced the shortest bowel evacuation time (31.5 min). The mean evacuation time after application of suppositories was 46.5 min after mineral oil, 57.6 min after glycerin, and 63.5 min after bisacodyl suppositories. DWE symptom scores also showed that docusate sodium was better than the other modalities.

Conclusions: This study shows that docusate sodium improves DWE symptoms and reduces total CTT more than the other modalities. This efficacy appears to be due to its effect on left segmental CTT. Docusate sodium was also associated with less patient discomfort and prompter bowel evacuation. Docusate sodium, along with digital stimulation, appears to result in more optimal bowel care than other modalities in spinal cord injury patients.

GM6. Pulmonary Complaints in Subjects with Chronic Spinal Cord Injury. M. Lesser, D. R. Grimm, A. M. Spungen, W. A. Bauman, P. L. Almenoff. Departments of Internal Medicine and SCI Services, Veterans Affairs Medical Center, Bronx, NY, and the Department of Internal Medicine and Rehabilitation Medicine, Mount Sinai Hospital, New York, NY.

Statement of the Problem: The prevalence of respiratory symptoms in subjects with spinal cord injury has not been assessed in detail.

Methods: We administered a standard respiratory questionnaire (Ferris BG, Epidemiology Standardization Project. *Am Rev Respir Dis* 1978;118:2), modified for these subjects. Among 119 subjects interview, 19 had high quadriplegia (HQ:C5 and above not requiring mechanical ventilation), 36 had low quadriplegia (LQ:C6–8); 47 had high paraplegia (HP:T1–7), and 17 had low paraplegia (LP:T8–L3).

Results: Ages (mean $\pm$ SEM) of the subjects were HQ:43 $\pm$ 4, LQ:47 $\pm$ 2, HP:54 $\pm$ 2, and LP:55 $\pm$ 3. Duration of injury (years) was HQ:11 $\pm$ 3, LQ:17 $\pm$ 2, HP:24 $\pm$ 2, and LP:22 $\pm$ 3. The number of active smokers was HQ:32%, LQ:33%, HP:36%, and LP:29%. Fifteen (79%) of the subjects in the HQ group complained of occasional breathlessness, which was significantly higher ($p < 0.05$; ANOVA) than that found in the LQ (58%), HP (32%), and LP (41%) groups. Breathlessness occurred at rest (HQ:47%, LQ:17%, HP:6%, LP:6%), with exertion (HQ:47%, LQ:50%, HP:30%, LP:24%), and with exposure to cold air (HQ:21%, LQ:8%, HP:11%, LP:12%), hot air (HQ:53%, LQ:19%, HP:17%, LP:18%), cigarette smoke (HQ:42%, LQ:19%, HP:15%, LP:12%), perfumes (HQ:21%, LQ:6%, HP:11%, LP:12%), and hair spray (HQ:21%, LQ:3%, HP:15%, LP:12%). Six (32%) of the subjects in the HQ group complained of wheezing, which did not differ significantly from that found in the LQ (22%), HP (13%), and LP (18%) groups. Similarly, the number with chronic cough (HQ:26%, LQ:11%, HP:11%, and LP:29%), or chronic cough with phlegm (HQ:37%, LQ:19%, HP:15%, and LP:18%), did not differ significantly among the groups.

Conclusions: These findings demonstrate that breathlessness is a frequent complaint among subjects with high cervical injuries, and that symptoms are aggravated with exposure to cold air, hot air, and exogenous agents. The findings, combined with our previous observations that all subjects with quadriplegia are hyperresponsive to inhaled methacholine, and that pretreatment with ipratropium bromide blocks the methacholine response, suggest that long-term administration of a

bronchodilator could reduce the frequency of respiratory complaints in these subjects. In addition, bronchodilator-induced decrease in airway hyperreactivity could possibly attenuate symptoms related to inhalation of airway irritants.

Hematology

H1. Optimization of Retroviral Gene Transfer in Cord Blood Stem and Progenitor Cells Using Clinically Applicable Protocols. J. Asch[†], E. Weinberg[§], Y. Galperin[§], L. Kiang[§], M. Bodner[@], S. Chang[@], D. Jolly[@], L. Isola[§]. [†]Division of Pediatric Hematology Oncology, Department of Pediatrics, [§]Division of Hematology, Department of Medicine, Mount Sinai School of Medicine, New York, NY, and [@]Viagene, San Diego, CA.

Statement of the Problem: This study assesses optimal conditions for the transfection of a retroviral vector carrying a marker gene into umbilical cord blood (CB) progenitor/stem cells (P/SC). CB contains P/SC with high proliferative capacity, is generally discarded, and can be harvested without risk to the mother or infant. Thus, CB is an ideal target for early gene therapy.

Methods: Since most transduction protocols have been developed in adult P/SC we examined the influence of red cell separation, CD34⁺ enrichment, multiplicity of infection (MOI) and polycations on the efficiency of transduction of CB P/SC. CB mononuclear cells (MNC) were enriched for CD34⁺ and transduced with a LacZ amphotropic retroviral vector at MOI of 1–20. Transduction media contained fetal calf serum or autologous plasma, polycations, and human growth factors. Efficiency of transduction was determined by X-gal stain and PCR assays.

Results: Cell recovery data (mean $\pm$ SD): CB volumes: 88 $\pm$ 28 ml, column yield: 3.5 $\pm$ 4.9 $\times 10^6$ cells, CD34⁺ purity: 33 $\pm$ 27%. Efficiency of transduction: Liquid cultures (X-gal stain) 8.8–63%, hematopoietic colonies 63–72% (PCR) and 56% (X-gal stain). The X-gal stain yielded false-positive results in cell colonies. For MNC separation, dextran sedimentation was superior but ficoll-hypaque results in higher CD34⁺ purities. Para-magnetic bead technology resulted in the best CD34⁺ enrichments (up to 93.8% CD34⁺). Vector MOI ≥ 10 , supplementation of the transduction media with polybrene 2 μ g/mL and 10% autologous plasma yield the highest efficiency of transduction.

Conclusions: Using purified retroviral stocks and standard CD34 selection technology, we achieved gene transfer efficiencies in CB P/SC similar to those reported in adult bone marrow and peripheral blood stem cells using crude retroviral supernatants.

H2. Adeno-Associated Virus (AAV) Gene Transfer of the Human γ -Globin Gene into Normal Human Bone Marrow Progenitor/Stem Cells (P/SC). R. S. Weinberg¹, J. Asch², Y. Galperin¹, L. Kiang¹, L. Isola.¹ ¹Division of Hematology, Department of Medicine, ²Division of Hematology Oncology, Department of Pediatrics, Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: Hemoglobin in human fetuses and neonates contains >50% γ -globin (of γ + β globin chains), whereas adults synthesize <1% γ -globin. Increased γ -globin synthesis may ameliorate hemoglobinopathies such as sickle-cell disease and β -thalassemia. The purpose of this study was to increase γ -globin synthesis in normal adult bone marrow (BM) progenitor/stem cells (P/SC) by gene transduction with an AAV type 2 vector containing the human γ -globin gene. AAV is a nonpathogenic human parvovirus with limited capacity to carry foreign DNA (up to 4.5 kb), which may be useful for P/SC transduction because it (1) can be manufactured in very high titers, (2) is nonpathogenic, (3) may be able to infect cells that are not dividing, and (4) may

integrate within a defined region of the cellular genome, reducing the risks of insertional mutagenesis. The ultimate goal is to develop gene therapy protocols for patients with hemoglobinopathies.

Methods: The clinical grade, high titer γ -globin AAV vector (7×10^{13} DNA particles/mL or 2×10^{11} infectious particles/mL) used carries the human β -globin locus control region (LCR) driving the expression of a genomic human γ -globin construct. For transductions, 5×10^5 BM CD34+ cells were incubated in 4 mL of a medium with 10% fetal bovine serum, hematopoietic growth factors (HGFs, IL-6, IL-3, SCF, GM-CSF), and AAV vector (either 60 or 6 particles/cell) for 48 hours. Cells were then transferred to methylcellulose medium with erythropoietin and HGFs to evaluate transduction of progenitor cells or to long-term culture medium (LTCM) for up to 4 weeks. Weekly, cells were transferred from LTCM to methylcellulose to evaluate long-term culture initiating cells (LTC-IC, i.e., immature P/SC). After 2 weeks in methylcellulose, individual hemoglobinized (red) colonies were removed, incubated with ^3H -leucine for 16 hours, and globin synthesis was analyzed by polyacrylamide gel electrophoresis and fluorography. Analysis by reverse transcriptase polymerase chain reaction (RT-PCR) for incorporation of the γ -globin gene is pending.

Results: The ratio of γ -globin synthesis ($\gamma + \beta$) in control BFU-E-derived colonies ranged from 3% to 22% (mean ± 1 SD = $12 \pm 7\%$). γ -Globin synthesis in 14 of 17 colonies from cells cultured with AAV ranged from 0% to 23% (mean = $9 \pm 8\%$). In contrast, 3 of 17 colonies (17.6% of colonies) transduced with AAV synthesized 29–44% γ -globin (mean = $36 \pm 8\%$). Mean γ -globin synthesis in these transduced colonies was significantly greater than in control BFU-E ($p = 0.000045$) and other BFU-E derived from cells exposed to AAV ($p = 0.000058$). γ -Globin synthesis data for LTC-IC derived colonies are pending.

Conclusions: AAV vectors can successfully transduce the human γ -globin gene into human BM progenitor cells, and γ -globin gene expression can be increased in approximately 20% of colonies derived from transduced progenitor cells.

H3. Platelet Glycoprotein (GP) IIb Missense Mutation, LEU183PRO, Resulting in Glanzmann Thrombasthenia. D. L. French, F. Chen, V. Najfeld, H. J. Weiss, B. S. Coller. Divisions of Hematology, St. Lukes-Roosevelt and The Mount Sinai Hospital, New York, NY.

Statement of the Problem: Glanzmann thrombasthenia is an inherited bleeding disorder due to absent or dysfunctional platelet $\alpha_{\text{IIb}}\beta_3$ (GPIIb/IIIa) integrin receptors.

Methods: Based on prolonged bleeding time and absence of platelet aggregation in response to ADP, a 53-year-old white male was diagnosed in 1961 as having Glanzmann thrombasthenia. The patient has had a lifelong history of severe epistaxis, excessive bruising, and bleeding after trauma and tooth extractions. The surface expression of platelet-specific receptors, GPIIb/IIIa and GPIb, and the expression on platelets of the more widely expressed vitronectin receptor $\alpha_v\beta_3$, which uses the same β_3 chain as $\alpha_{\text{IIb}}\beta_3$, were analyzed using radiolabeled monoclonal antibodies (mAbs). GPIIb/IIIa was analyzed using complex-dependent mAbs.

Results: Expression of GPIIb/IIIa was markedly decreased [mAb 10E5 (2.6% of normal) and mAb 7E3 (5.4% of normal)]. The expression of GPIb was normal [mAb 6D1 (108% of normal)]. The expression of $\beta_v\beta_3$ was increased [mAb LM609 (a gift of Dr. David Cheresh, Scripps) (192% of normal)], suggesting that the patient expressed a normal β_3 chain and that the defect in the patients' GPIIb/IIIa receptor was in the α_{IIb} chain (GPIIb). Immunoblotting of GPIIb with mAb PMI-1 (a gift of Dr. Mark Ginsberg, Scripps) showed a small amount of normally migrating GPIIb (M_r 140,000, nonreduced) and a possible fragment of GPIIb at M_r 120,000. Only $\sim 3/4$ of the GPIIb band decreased to M_r 120,000 with reduction, suggesting that the remaining fourth was uncleaved, pro-GPIIb. In addition, a fragment of $M_r \sim 98,000$ was present, which could represent loss of the GPIIb light chain from the originally observed fragment.

Results: Using ten pairs of GPIIb-specific oligonucleotide primers, reverse transcription and polymerase chain reaction (RT-PCR) amplification of the patients' platelet RNA was performed. A single mutation was identified, T to C at nucleotide 6421, predicting a Leu183Pro substitution. This mutation was confirmed by single-strand and confor-

mation polymorphism (SSCP) analysis and direct sequencing of exon 6 using PCR amplified DNA. Since consanguinity was denied, analysis of the genes encoding GPIIb were performed by Southern blot and fluorescence in situ hybridization (FISH) using a GPIIb cDNA probe (kindly provided by Dr. Peter Newman). These analyses suggested a large deletion in one allele. Thus a deletion in one GPIIb allele and a mutation in the other results in functional homozygosity for the mutation.

Conclusions: The GPIIb Leu183Pro mutation is probably responsible for the Glanzmann thrombasthenia in this patient. This mutation is likely to prevent normal complex formation between GPIIb and GPIIIa and may increase the susceptibility of GPIIb to proteolysis near the mutation site.

H4. Glanzmann Thrombasthenia Resulting from a Cysteine Mutation in Platelet Glycoprotein (GP) IIIa. C. M. Grimaldi, F. Chen, B. S. Coller, D. L. French. Division of Hematology, SUNY at Stony Brook, and The Mount Sinai Hospital, New York, NY.

Statement of the Problem: Glanzmann thrombasthenia is an inherited bleeding disorder characterized by a quantitative or qualitative abnormality of platelet GPIIb and/or GPIIIa.

Case Report and Methods: A 20-year-old female from a consanguineous family in Hunan Province of the People's Republic of China was diagnosed as having Glanzmann thrombasthenia based on: (1) a nearly lifelong history of epistaxis, gum bleeding, petechiae, and purpura; (2) severe menorrhagia resulting in anemia and need for whole blood transfusion; (3) normal coagulation assays; (4) prolonged bleeding time; (5) absent clot retraction; (6) decreased glass bead retention; (7) absent platelet aggregation in response to ADP, epinephrine, and collagen; and (8) normal initial slope of platelet aggregation in response to ristocetin, but with a diminished maximal extent. The patients' platelets had a decreased level of platelet fibrinogen, but the deficiency was not as severe as in other patients with this disease. Platelet surface GPIIb/IIIa expression was $<15\%$ of normal, as judged by monoclonal antibody binding studies. Immunoblotting demonstrated a marked decrease in GPIIIa and a moderate decrease in GPIIb. Interestingly, the GPIIb had undergone normal processing into GPIIb α and GPIIb β , suggesting some normal complex formation of the two chains. The complete sequence of the patient's GPIIIa RNA was determined, and the only identified mutation was a G to A mutation at nucleotide 1219, predicting a Cys to Tyr substitution at residue 374.

A number of point mutations have been identified in the GPIIIa gene in patients with Glanzmann thrombasthenia, but no single cysteine mutation has been reported, even though GPIIIa is notable for having 56 cysteines in which 31 are clustered into four randomly repeated segments. Introducing this mutation into a GPIIIa cDNA construct and cotransfection with GPIIb in Chinese hamster ovary (CHO) cells resulted in an approximately 90% reduction in GPIIb/IIIa surface expression. Single-strand conformation polymorphism (SSCP) analysis and direct sequencing of PCR amplified cDNA and GPIIIa exon VIII indicated that the patient is homozygous and her parents heterozygous for the mutation.

Results: These data indicate that the Cys374Tyr mutation in GPIIIa is the probable cause of Glanzmann thrombasthenia in this patient.

Conclusions: The normal processing of GPIIb and the relative mildness of the defect in platelet fibrinogen raise the possibility that some GPIIb can complex with the mutant GPIIIa and that the complex can be transported to the platelet surface and bind fibrinogen. Stable CHO cell lines have been generated to directly test these possibilities. One hypothesis that may account for these findings is that the GPIIb/IIIa complex becomes unstable as it cycles from the surface to α -granules and back to the surface.

H8. Hemorrhagic Cystitis following Bone Marrow Transplantation (BMT). Melanie Austin, Eileen Scigliano, M.D., Douglas Birns, M.D., Luis Isola, M.D., Adrianna Vlachos, M.D., Steven Fruchtman, M.D.

Division of Hematology and Department of Urology, The Mount Sinai Hospital, New York, NY.

Statement of the Problem: Hemorrhagic cystitis (HC), a potentially life-threatening complication associated with the use of high-dose intravenous cyclophosphamide (CY), is seen in up to 50% of patients undergoing BMT. HC results from the toxic effects of acrolein, a metabolite of CY, on bladder epithelium. Interventions designed to prevent this complication, including hyperhydration, continuous bladder irrigation, and administration of 2-mercaptoethane sodium sulfonate (mesna), a chemical which binds to acrolein, have met with varying success.

Methods: Of 188 patients undergoing allogeneic or autologous BMT at The Mount Sinai Hospital, 13 developed severe HC (6.9%), defined as macroscopic hematuria with clots requiring intervention, including transfusion, continuous bladder irrigation, or formalin instillation. All patients received prophylactic treatment, including vigorous hydration, forced voiding, and mesna at 160% of the CY dose.

Results: The 9 female and 4 male patients developed HC a median of 20 days following BMT. The median age was 39 years for the 7 patients undergoing autologous BMT and 29 years for the six patients undergoing allogeneic BMT. Supportive care included transfusion with packed red blood cells (a mean of 23.5 units/patient, compared to a mean of 9 units/patient for an age/diagnosis matched control group of patients who did not develop HC) and platelets (a mean of 112.5 units of pooled platelets vs. 59.3 units for the control group) as well as continuous bladder irrigation with normal saline (in 10 patients).

Five patients were treated with bladder instillation of 2%–4% formalin at a median of 24 days following the onset of HC because of persistent, severe hemorrhage. HC resolved in all patients but one, who died of unrelated causes. No patients undergoing formalin instillation have developed ureteral strictures or low-capacity, noncompliant bladder, which are known complications of this intervention.

Conclusions: (1) Hemorrhagic cystitis remains a major complication of BMT, (2) Patients with HC require a significantly greater use of blood products, (3) Formalin instillation is an effective therapeutic intervention, (4) Controlled trials are needed to study the role of earlier instillation of formalin, since long-term complications appear to be minimal.

H9. Atheromatous Plaque Extracts Have Constitutive Tissue Factor Activity (TFa) and Induce TFa in Monocytes. Platelet Aggregation and Monocyte Chemotaxis Are Also Induced. T. Muhlfelder, V. Teodorescu, J. Rand, J. Niemetz. Section of Hematology/Oncology and Surgical Service, Bronx VA Medical Center and The Mount Sinai Hospital, New York, NY.

Statement of the Problem: It is now accepted that plaque rupture triggers thrombosis in atheromatous vessels. Tissue factor activity (TFa) is a major activator of the coagulation cascade and may play a role in atheroma-induced thrombosis. Monocyte macrophages (MO-MF) generate considerable quantities of TFa when stimulated by a variety of inducers. Moreover, MO are the only circulating blood cells to do so in vivo.

Methods: To test the hypothesis that MO could be induced by atheromatous plaque to generate TFa, plaques were obtained under sterile conditions at surgery from patients with obstructive atherosclerotic disease and were extracted in 0.9% NaCl. These extracts were tested for constitutive and induced TFa.

Results: The constitutive activity was variable from extract to extract but could be very high, up to 250 U TFa. The induced TFa was determined after incubating plaque extract with peripheral blood mononuclear cells (MN) and the TFa generated by MN assayed. This induced TFa could be also very high, up to 200 U (i.e., 1/5 of the TFa of full-strength rabbit-brain thromboplastin (TF)). However, induced and constitutive TFa correlated poorly with each other. TF antigen was localized in atheromatous plaque mainly around cholesterol clefts and in round cells—presumably macrophages. Plaque extract had also a chemoattractive effect for MO. Platelet aggregation was also induced by extracts in several cases.

Conclusions: Since macrophages may constitute up to 60% of cells in atheromatous plaque, they may be the source of most, if not all, plaque TFa. When plaque rupture occurs, newly attracted monocytes also generate TFa, which may be further potentiated by aggregating platelets.

H10. Fibrinogen Lacking the B β -Chain 1-42 Amino Acids Supports Platelet Adhesion, Aggregation, and GPIIb/IIIa ($\alpha_{IIb}\beta_3$) Receptor Redistribution. Keith A. Moskowitz, Lesley E. Scudder, and Barry S. Collier. Department of Medicine, Mount Sinai Medical Center, New York, NY.

Statement of the Problem: Platelet spreading on fibrin has been reported by Francis et al. to require cleavage of fibrinopeptide B and sequences putatively localized between residues B β 15 and B β 42.

Methods: To further study the structural requirements for the interaction between platelets and fibrinogen, we prepared a unique fibrinogen derivative lacking residues B β 1-42 (des B β 1-42) by cleaving plasma fibrinogen with *Crotalus atrox* protease III.

Results: Fibrinogen lacking B β 1-42 supported aggregation of gel-filtered platelets by 20 μ M ADP to the same extent as native fibrinogen, both showing the same dose dependence at concentrations from 50 to 500 μ g/mL. Binding of platelets labeled with ^{51}Cr to microtiter plates coated with either native or des B β 1-42 fibrinogen at 3 to 33 μ g/mL was similar, suggesting that platelet adhesion to fibrinogen is not mediated by B β 1-42. We previously reported that platelets that adhere to and spread on high-density immobilized fibrinogen lose their ability to bind thromboerythrocytes (erythrocytes with $\sim 10^6$ RGD-containing peptides on their surface), suggesting redistribution of GPIIb/IIIa from the luminal to the albuminal surface. Platelets adhering to des B β 1-42 fibrinogen demonstrated the same phenomenon.

Conclusions: Our results suggest that the first 42 amino acids in the B β -chain of fibrinogen are not required for fibrinogen-mediated platelet adhesion, aggregation, or GPIIb/IIIa receptor redistribution.

Infectious Diseases

ID1. Orthostatic Hypotension, AIDS, and Hypoaldosteronism. Ahmad L, MD, Masci J, MD, Policar M, MD, Shimshi M, MD. Elmhurst Hospital Center and Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: We have previously identified five patients with AIDS and isolated hypoaldosteronism. The only consistent finding in these patients (pts) was orthostatic hypotension (OH). This study attempts to determine the significance of orthostatic hypotension as an indicator of hypoaldosteronism.

Methods: Outpatients with AIDS and a CD4 count ≤ 100 were included. Pulse and blood pressure (BP) were measured on pts in supine and upright positions. OH was defined as (1) systolic BP decrease ≥ 20 , (2) diastolic BP decrease ≥ 10 , or (3) pulse increase ≥ 20 . Subsequent ACTH stimulation testing was done on patients with OH. Baseline renin and aldosterone response to ACTH were also measured.

Results: Of the 91 patients evaluated, 4 patients were excluded (2 were receiving steroids, and 2 were undergoing hemodialysis). Of the remaining 87 pts, 44 had OH. Of these 44 pts, we were able to perform ACTH stimulation tests on 25 (57%).

Cortisol response to ACTH stimulation was normal in 24 of 25 pts (96%). The one pt with an abnormal cortisol response was asymptomatic and had normal serum electrolytes. This pt had a normal aldosterone (aldo) response to ACTH stimulation and normal baseline renin activity.

Four of the 25 pts (16%) who underwent ACTH stimulation testing had an inadequate aldo response; however, cortisol levels were normal.

None of the 4 pts had any electrolyte abnormalities; 3 complained of lightheadedness. Baseline renin activity was abnormally low in all 3 symptomatic pts.

Conclusions: In AIDS pts with $CD4 \leq 100$, OH may be due to hypoadosteronism. Pts with hypoadosteronism may not be distinguished from those with normal or high levels of aldo on the basis of serum electrolytes, or baseline or stimulated cortisol levels. Abnormal aldo secretion may result from inadequate renin production.

ID2. The Risk of Fungemia in Patients Receiving Peripheral Parenteral Nutrition. Hormozdi S, Policar M, Schechter C. Elmhurst Hospital Center, Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: The use of total parenteral nutrition (TPN) has been associated with the development of candidemia. The administration of peripheral parenteral nutrition (PPN) has not been associated with this infection, and is considered to be a safe and noninvasive method of providing nutrition. We evaluated the risk of fungemia in patients receiving PPN, and compared this with the risk associated with receiving TPN.

Methods: Pharmacy records of patients receiving parenteral nutrition solutions were reviewed and compared with microbiology lab records on blood culture results.

Results: A total of 408 patients received either TPN or PPN over a 33-month period. Twenty-four patients who had received both solutions were excluded from the study. Of 263 patients receiving TPN, 27 (10.3%) had blood cultures positive for *Candida* temporally related to the administration of TPN. Of the 145 patients receiving PPN, 10 (6.9%) had blood cultures positive for *Candida* temporally related to PPN administration.

Conclusions: Using the chi-square test, we found no statistically significant difference between the risk of candidemia associated with PPN administration and the risk associated with TPN administration. It may be necessary to reconsider the use of PPN in certain situations, given the newly recognized risk of candidemia.

ID3. Ocular Complications in Orthotopic Liver Transplant (OLT) Patients: Diagnostic and Therapeutic Strategies. B. R. Meyers, G. A. Papanicolaou, M. H. Mendelson, W. Fuchs, S. Guillory, P. Sheiner, C. Miller. Division of Infectious Diseases and Transplantation, The Mount Sinai Hospital, New York, NY.

Statement of the Problem: Infectious ocular complications (OcCp) occurred in 9/684 patients (pts) who received OLT from 9/3/88 to 11/9/94.

Methods: Three pts had endophthalmitis (endop), 2 from *Candida* (C) and 1 from *Aspergillus*. Four had cytomegalovirus (CMV) retinitis (ret), 1 had herpetic keratitis (HSV), and 1 had varicella panophthalmitis (VZV). Mean (mn) age was 47.2; there were 4 females and 5 males. Indications for OLT were hepatitis (h) C (3), biliary cirrhosis (2), alcoholic cirrhosis (2); 1 with h C, fulminant hepatic failure (1), autoimmune h (1). Immunosuppression: triple drug (td) (3), OKT3 plus td (1), Tacrolimus/prednisone (2), prednisone/CSA (3); 5 pts had rejection.

Results: Diagnosis (dx) of fungal (f) infection (inf) was made by gram stain of vitreal aspiration (vit asp) in 2; 1 *C. albicans*; 1 *Aspergillus*; + blood cultures, *C. albicans* (1); disseminated aspergillosis at autopsy (1). 1 pt with CMV ret had concurrent CMV pneumonia. Mn time from OLT to presentation: 32 days (d) for f inf; 128d for viral inf. 5/9 with blurred vision, 2/9 ocular pain, 2/9 bilateral disease; *C. albicans* endop (1), CMV ret (1). F endop treatment (t): Amphotericin B dose range 1–2G. CMV inf t: ganciclovir (mn) dose 287.5 mg/d for (mn) 23d; in 1 pt IV gammaglobulin was used. HSV inf t: acyclovir 200mg 5x/d for 2 weeks and ganciclovir 300mg/d x 21d for concurrent CMV colitis. VZV inf t: acyclovir 1800mg/d x 21d. 2/4 CMV-pts with CMV ret, received CMV + organ. Mn follow-up was 2 yrs (9d to 5 yrs). Permanent vision loss occurred in 3 (CMV 2, VZV 1); 5 had visual acuity improvement (range 20/100–20/30).

Conclusions: (1) Infections should be suspected in every transplant

patient with OcC symptoms or with systemic disease that may affect the optic fundus; (2) f inf occurs early (mn) 1 month; viral at (mn) 4 months; (3) aggressive diagnostic work-up and timely treatment are essential for preservation of vision; (4) lifelong maintenance therapy with antiviral agents may not be required.

ID4. Orthotopic Liver Transplant (OLT) in Patients with Recent Spontaneous Bacterial Peritonitis (SBP): Correlation of Length of Treatment and Laboratory Parameters to Outcome. B. R. Meyers, G. A. Papanicolaou, M. H. Mendelson, P. Sheiner, C. Miller. Division of Infectious Diseases and Transplantation, The Mount Sinai Hospital, New York, NY.

Statement of the Problem: Factors determining optimum time to perform OLT, following SBP, in order to prevent complications due to postoperative infections (PI) are not known.

Methods: Thirteen patients (pts) with SBP occurring within 28 days (d) pre-OLT from 1990 to 1994, were analyzed.

Results: There were 4 females, 9 males; mean (mn) age 55.4 years. PI rate was 38.4%. Pre-op diagnoses included alcoholic cirrhosis (6), hepatitis C (3), primary biliary cirrhosis (2), and other (2). Mn UNOS status was 3.3. Diagnostic peritoneal aspiration (asp) was performed between d 4 and 27, (mn) 11.2d. Mn white blood cells (WBC)/mm³ were 7140, (range, 450–48400). Mn polymorphonuclear leukocytes (PMNs) were 63% (range, 23–98) and (mn) absolute neutrophil count (ANC) was 3289 (range, 270–10509). A repeat asp was done in 11 of 13 pts pre-OLT; (mn) 3.6d (range, 1–7). Mn WBC/mm³ in the follow-up asp was 308.5d (range, 15–490). Mn PMNs 32% (range, 3–74). Mn ANC 97 (range, 0–310). Initial asp cultures (cul): *E. coli* (5), *S. aureus* (2), *K. pneumoniae* (1) *Streptococcus intermedius* (1), *Enterobacter* sp. (2), negative cul (2). Blood cul pre-op were positive in 2/13 (*E. coli*). Mn therapy (th) pre-OLT 16d (range, 4–50). Outcome: All patients had sterile peritoneal fluid at the time of OLT. 5/13 (38.4%) pts developed PI; *Candida* peritonitis (2), subhepatic abscess with *S. aureus* (1), intraabdominal sepsis with negative cul (2). 4/5 pts required reexploration; 3/5 died of early postoperative sepsis (2), hepatic artery rupture (1).

Conclusions: (1) Rate of PI was 38.4%, though all pretransplant asp cul were sterile. (2) Th of SBP pre-OLT was longer in PI group (mn) 20.6 d vs without (mn) 8.9d. (3) SBP due to *S. aureus* was associated with PI or death. (4) PIs were not related to time from SBP to OLT, (mn) number of WBC, or PMNs present in last asp examined.

ID5. Intra-Abdominal Infections after Orthotopic Liver Transplantation (OLT): Epidemiology and Risk Factors Associated with Mortality. B. R. Meyers, G. A. Papanicolaou, M. H. Mendelson, P. Sheiner, C. Miller. Division of Infectious Diseases and Transplantation, The Mount Sinai Hospital, New York, NY.

Statement of the Problem: Infection is the most common cause of death in solid organ transplant pts. We analyzed factors associated with mortality during a 2-year period from 1/93 through 12/94.

Methods: 293 pts received 352 OLTs. 95 pts (32.4%) who developed intra-abdominal (ID) infection had 210 infectious episodes (IE); rate 2.2 IE/pt. Indications for OLT for infected pts (IP): alcoholic hepatitis (alc) 14; Hep C 24; alc plus hep C 5; primary biliary cirrhosis 13; cryptogenic cirrhosis 10; others 29. Induction immunosuppression for IP: tacrolimus 20; OKT3 20; triple drug regimen 43 and retransplantation 31 pts (32.6%). Early inf <2 weeks post OLT 47 pts (49%); 81 IE rate 1.7 IE/pt.

Results: Infectious episodes: abscess 31, fasciitis 38, peritonitis 77, cholangitis 13. Incidence of fungal inf 19/95 (20%); associated blood stream infection (BSI) 44 pts (46.3%); polymicrobial BSI 14 pts (31%). Most common organisms of BSI: vancomycin-resistant *Enterococcus faecium* (VREF) (11); *Ps. aeruginosa* (10); *K. pneumoniae* (10); *Enterobacter* spp. 7 methicillin-resistant *S. aureus* (MRSA) (6). Total microbial isolates: VREF 64, MRSA 31; *Enterobacter* spp. 30; *K. pneumoniae* 35; *Ps. aeruginosa* 27; *Candida* spp. 28. Mortality: 44 patients died 34/44 (77%) from infection; 32/44 (73%) had BSI.

Conclusions: Mortality for IP was associated with (1) blood stream infection ($p < 0.0001$); (2) polymicrobial blood stream infection ($p < 0.05$); (3) *Pseudomonas* infection ($p < 0.05$); (4) fungal infection ($p < 0.1$); (5) retransplantation ($p = 0.1$). Mortality was not associated with use of tacrolimus or OKT3 antibodies.

ID6. An Analysis of Sharps Injuries (SIs) in the Operating Room: A Prospective Study of 590 Intraabdominal Procedures. M. H. Mendelson, J. Cunningham, R. Solomon, B. Rynne, J. Solomon, G. Kogan, J. Godbold, M. Hirshon, B. Meyers, and S. Hirschman. The Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: To establish a baseline SI rate prior to the investigation of blunt suture needles for general surgical intraabdominal procedures, a prospective surveillance study was performed at an 1100-bed metropolitan university medical center.

Methods: From 12/94 to 6/95 a SI surveillance form was completed by OR circulating nurses and confirmed by scrub nurses. Of 590 cases surveyed, 88 (14.9%) were co-observed by a dedicated observation nurse. 564 (95.6%) were elective, 26 (4.4%) were urgent/emergent, and the duration of cases ranged from 0.15 to 13.7 (mean, 2.7) hrs. Surgical devices utilized to prevent SIs included skin staplers in 396 (67%) and intraabdominal staplers in 341 (58%) cases.

Results: There were 18 SIs in 590 cases (SI rate, 3.2%): 9 suture needles (8 conventional tapered), 3 bovie, 1 scalpel, 1 hollowbore needle, 1 rake retractor, and 3 unspecified. SIs were incurred by 8 attending surgeons, 6 house officers, 3 medical students, and 1 scrub nurse. Activities at the time of injury included 5 during suturing, 2 holding/retracting tissue, 3 inadvertently by stray sutures (2 in surgical field, 1 on OR table), 2 cutting/coagulating, 1 returning retractor, 1 injecting, and 3 unknown. There was no difference in the use of staplers, urgency of cases, or mean duration of surgery in procedures with SIs vs. those without. The injury rate for co-observed cases was 5.8% (5/88).

Conclusions: General surgical intraabdominal procedures are associated with a significant risk of SIs which may be underestimated by a surveillance system dependent on OR personnel. If proven applicable, blunt suture needles have the potential to prevent up to 44% of SIs in this setting.

ID8. Inducible Nitric Oxide Synthase Is Not Expressed in Stimulated Guinea Pig Macrophages with or without BCG Vaccination. S. T. Brown, G. Almeida, H. Doo, I. Brett, S. He, J. L. Ho. Infectious Disease Section, Bronx VAMC, Mount Sinai School of Medicine, New York, NY, and Division of International Medicine, Cornell University Medical College, NY.

Statement of the Problem: The absence of inducible nitric oxide synthase (iNOS) activity in human macrophages (M Φ), but its ready induction at high levels in murine M Φ , may contribute to the greater susceptibility of humans to infection with *M. tuberculosis*.

Methods: We compared the capacity to induce iNOS activity in guinea pig (GP) alveolar M Φ (ALM), GP thioglycolate elicited peritoneal lavage M Φ (PEM), and a murine M Φ cell line, RAW 264.7. Cells were stimulated with lipopolysaccharide @ 2.5 μ g/mL (LPS), recombinant human (Hu) or murine (Mu) IFN- γ @ 1000 U/mL, conditioned media from PHA stimulated lymphocytes (LCM), or LPS + Hu rIFN- γ , + Mu rIFN- γ , or + LCM. Supernatants were harvested and assayed for nitrite or for production of superoxide.

Results: GP PEM and ALM produced no more nitrite than media control after stimulation for 24, 48, and 72 hours. RAW cells produced large quantities of nitrite after stimulation with LPS and/or Mu rIFN- γ , but iNOS activity was not stimulated by Hu rIFN- γ . Activation of M Φ , shown by upregulation of superoxide production, was seen from GP M Φ treated with LCM but not with recombinant IFN- γ 's. After GP were vaccinated or vaccinated/boosted with BCG, no nitrite was produced by PEM incubated in media with or without LPS, despite show-

ing a vigorous respiratory burst. Primers common to a conserved region of human and mouse iNOS were used in reverse transcriptase PCR of GP PEM from thioglycolate elicited from BCG vaccinated animals. Amplified products of the expected size were found from both conditions.

Conclusions: Therefore, while GP M Φ are similar to human M Φ in their lack of iNOS production following conventional stimuli, there is preliminary evidence for transcription of iNOS from in vivo stimulated GP M Φ .

ID9. In Vitro Inhibitory and Bactericidal Activity of Fleroxacin against Clinical Isolates of *Mycobacterium tuberculosis*. A. Shahidi, S. D. Park, and S. T. Brown. Clinical Microbiology Laboratory and Infectious Disease Section, VA Medical Center, Bronx, NY, and Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: Fleroxacin is a novel fluoroquinolone agent with an obtainable serum concentration of 4 μ g/mL and a long half-life of elimination.

Methods: The activity of fleroxacin against clinical isolates of *M. tuberculosis* was evaluated by standard broth radiometric methods (BACTEC). Two reference strains and 18 clinical isolates, with varying susceptibilities to conventional antimycobacterial agents, were tested at 8, 4, 2, 1, and 0.5 μ g/mL of fleroxacin.

Results: The MIC₅₀ and MIC₉₀ were 2 and 2–4 μ g/mL, respectively, and the range was 1–4 μ g/mL. Resistance to other agents did not affect susceptibility to fleroxacin. Bactericidal levels were within one dilution of the MIC for all isolates.

Conclusions: Fleroxacin's significant antituberculous activity combined with its favorable pharmacokinetic profile make it an attractive candidate for further clinical evaluation.

Liver

L3. Role of the Template Bleeding Time in Predicting Bleeding Complications of Percutaneous Liver Biopsy. DC Wolf¹, F Weber², J Palascak², D Hanto², C Bodian¹, and RA Giannella². ¹Mount Sinai Medical Center, New York, NY, and ²University of Cincinnati Medical Center, Cincinnati, OH.

Statement of the Problem: Prolongation of the template bleeding time (BT) has been proposed as a risk factor for bleeding after invasive procedures, including percutaneous liver biopsy (PLB). Our aim was to assess prospectively the influence of BT on the occurrence of bleeding after PLB.

Methods: BTs were determined immediately prior to 273 PLBs performed at Univ. of Cincinnati between June 1992 and October 1994. PLBs were performed in patients with a platelet count $\geq 60,000/\text{mm}^3$ and a prothrombin time < 16 seconds. Elevated BTs were not corrected with DDAVP or blood products prior to PLB. Bleeding events were characterized by the need for urgent blood transfusion and were confirmed by CT scan.

Results: A total of 188 PLBs (1–12 per patient) were performed in 62 patients who had undergone orthotopic liver transplantation (OLT). The median BT was 6.25 minutes (range 1.5–19.0). 147 PLBs were performed when the BT was < 10 . Bleeding complications followed 1 PLB (0.7%) in a patient with a BT of 7.5. 41 PLBs were performed when the BT was ≥ 10 . Bleeding followed 2 PLBs (4.9%) in patients with BTs of 15.5 and 17.5.

A total of 79 PLBs were performed in 77 non-OLT patients with no evidence of end-stage renal disease (ESRD). The median BT was 4.0 minutes (range 2.0–13.5). This was significantly lower than the BT in OLT patients ($p < 0.001$). Two PLBs (2.5%) were performed when the

BT was ≥ 10 . No bleeding complications occurred in these non-OLT patients.

6 PLBs were performed in 5 non-OLT patients undergoing treatment for ESRD with hemodialysis. The median BT was 6.75 minutes (range 4.0–20.0). 1 PLB (16.7%) was performed when BT was ≥ 10 . Bleeding followed 3 PLBs (50%) in 3 patients whose BTs were 4.0, 8.0, and 20.0 minutes.

Conclusions: OLT patients with a BT ≥ 10 minutes had a higher incidence of bleeding after PLB than patients with a BT < 10 minutes. Abnormal BT may be useful in identifying patients at increased risk of bleeding complications. However, the sample sizes of both the OLT and the non-OLT/non-ESRD patient groups were too small to draw a firm conclusion about BT and risk of bleeding after PLB. ESRD patients on hemodialysis are at high risk of bleeding complications after PLB, independent of BT.

L4. Effects Of Ethanol on Mitochondrial Aspartate Aminotransferase Expression and Leakage from Cells, and Fatty Acid Uptake in HepG2 Cells. S-L Zhou, C-L Kiang, M Bradbury, R Gordon, DD Stump, N-I Han, and PD Berk. Depts. of Medicine and Pathology, Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: Plasma membrane fatty acid binding protein (FABPpm), a long chain free fatty acid (FFA) transporter, is reported to be identical to mitochondrial (m) aspartate amino-transferase (AST) (AJP 264:G894). Alcoholic liver disease (ALD) is characterized by increased plasma AST $>$ ALT, whereas in most hepatic injury AST $<$ ALT. In ALD the elevated AST levels consist mainly of m-AST (Hepatology 4:893). This has been attributed to leakage from the morphologically abnormal mitochondria sometimes seen in this setting. However, increased plasma AST is often found without mitochondrial injury. Moreover, since m-AST leaking from mitochondria first enters the cytoplasm, it is unclear why m-AST should preferentially escape from the cytoplasm into the circulation.

Methods: To study this question, we established four long-term HepG2 cell cultures grown in 0, 20, 40, or 80 mM ethanol (EtOH). In these cultures, plasma membrane expression of FABPpm/m-AST was assessed by immunofluorescence, immunoelectron microscopy (EM), and Western blotting of plasma membrane extracts; mAspAT mRNA by slot blotting/scanning densitometry; AST leakage into the medium enzymatically; and mitochondrial morphology by EM. FFA uptake kinetics were quantitated with [^{3} H]-oleate.

Results: HepG2 cells at all EtOH levels displayed FABPpm/m-AST on the plasma membrane, with a progressive, EtOH related increase. This paralleled an increase in m-AST mRNA to $125 \pm 6\%$, $203 \pm 18\%$, and $248 \pm 13\%$ of control values (0 mM EtOH) at 20, 40, and 80 mM EtOH, respectively. Leakage of total AST into the culture medium per 24 hours was similar in cells cultured in 0 and 20 mM EtOH, but was increased 6- and 14-fold, respectively, in cells cultured at 40 and 80 mM EtOH. No gross alterations in mitochondrial morphology were observed by EM at any EtOH concentration studied. The Vmax for oleate uptake at 0, 20, 40, and 80 mM EtOH was 4.7 ± 1.8 , 4.2 ± 0.7 , 8.0 ± 1.7 , and 11.0 ± 1.9 pmol/sec/mg protein, respectively, and was highly correlated with mAspAT mRNA levels ($r = 0.97$; $p < 0.01$).

Conclusions: (1) EtOH upregulates m-AST synthesis and sorting to the plasma membrane; (2) increased plasma m-AST in ALD may be derived from plasma membrane FABPpm/m-AST, not mitochondria; and (3) increased plasma membrane FABPpm/m-AST mediates increased hepatocyte FFA uptake, which may be a contributing factor to alcoholic fatty liver.

L5. Upregulation of Mitochondrial Aspartate Aminotransferase mRNA Parallels Fatty Acid Uptake in 3T3-L1 Cells and Adipocytes from Obese and Diabetic Rats. S-L Zhou, C-L Kiang, M Bradbury, L Isola, DD Stump, and PD Berk. Dept. of Medicine (Divisions of Liver Diseases and Hematology), Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: Extensive data suggest that plasma membrane fatty acid binding protein (FABPpm), a putative long chain free fatty acid (FFA) transporter, is identical to mitochondrial aspartate aminotransferase (mAspAT) (AJP 264:G894). Sorting of FABPpm/mAspAT to the plasma membrane is highly regulated. Thus, the protein is detectable on the membrane of jejunal and ileal enterocytes, but not in stomach, duodenum, or colon (JCI 75:1068). Similarly, the Vmax for FFA uptake in 3T3-L1 cells increases by 40-fold during differentiation from a fibroblast to an adipocyte phenotype (JBC 267: 14456) and is highly correlated ($r = 0.99$) with densitometric quantitation of FABPpm and mAspAT antigens in Western blots of plasma membrane extracts (PSEBM 208:263) but not with mitochondrial mAspAT enzyme activity. We have reported (Hepatology 18:137A) that the Vmax for FFA uptake is selectively increased in adipocytes from Zucker obese (*fa/fa*) rats. We now report further studies in 8–12 week old adult male normal Wistar control (C), Zucker lean heterozygous (*fa/+*) and obese homozygous (*fa/fa*), and Zucker diabetic fatty (ZDF) rats.

Methods: Plasma glucose and FFA were measured enzymatically. FFA uptake Vmax was computed from studies of [^{3} H]-oleate uptake kinetics in isolated hepatocytes, cardiac myocytes, and adipocytes. mAspAT mRNA levels were estimated in these cells and in 3T3-L1 fibroblasts and adipocytes by slot blotting.

Results: Mean glucose levels were < 100 mg/dL in C, *fa/+*, and *fa/fa*, but increased to 368 ± 28 in ZDF. Mean plasma FFA were < 200 μ M in C and *fa/+*, 253 ± 39 in *fa/fa* and 470 ± 96 in ZDF. Vmax's and mAspAT mRNA levels were equivalent in hepatocytes from all 4 groups; Vmax's were unchanged in *fa/+* cardiac myocytes, but increased in *fa/fa* to 1.7- and in ZDF to 3 times C. Only in adipocytes was the Vmax in *fa/+* heterozygotes increased, to 1.4 times C ($p < 0.01$). Vmax's in *fa/fa* and ZDF adipocytes were markedly increased, to 9.3 and 11 times C, respectively. mAspAT mRNA levels in adipocytes correlated strongly with Vmax's ($r = 0.99$, $p < 0.01$). Similarly, mAspAT mRNA levels in 3T3-L1 adipocytes were 40–80 times those in fibroblasts.

Conclusions: In adipocytes and hepatocytes from obese and diabetic rats and in differentiating 3T3-L1 adipocytes, FFA uptake Vmax and mAspAT mRNA levels are highly correlated, supporting the postulated role of FABPpm/mAspAT as an FFA transporter.

L6: Mitochondrial Aspartate Aminotransferase Contains a 500 Å³ Hydrophobic Groove Representing a Putative Fatty Acid Binding Site. F Guarneri, DD Stump, J Roboz, Q Yu, and PD Berk. Depts. of Medicine (Liver Diseases and Neoplastic Diseases) and Physiology, Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: Extensive data indicate that plasma membrane fatty acid binding protein (FABPpm), a putative long chain free fatty acid (FFA) transporter, is identical to mitochondrial aspartate aminotransferase (mAspAT) AJP 265:G894. However, while FABPpm binds FFA with high affinity, purified mAspAT does not consistently bind exogenous [^{3} H]-FFA. Such binding is observed after passage over oleate-agarose affinity columns, as used during FABPpm isolation. By analogy with other proteins (BBRC 190:823), we postulate that this displaces endogenous FFA from a high affinity binding site, making it accessible to exogenous ligands.

Methods: To test this hypothesis and identify the proposed FFA binding site in mAspAT, we searched the Protein Data Bank for mAspAT crystal structures. Chicken heart mAspAT was chosen for further study because its published crystal structure has a resolution of 2.3 Å. This structure was read into the molecular modeling program Macromodel, version 4.5. The tertiary configuration of the α -carbon backbone was displayed as a ribbon diagram in which hydrophobic, charged hydrophilic, and uncharged hydrophilic residues were distinguished by color coding.

Results: Initial evaluation revealed a region densely packed with hydrophobic amino acids. Enlargement of this region, extending from residues 166–270, indicates that it includes both hydrophobic β strands and at least 3 α -helices in which hydrophobic residues are directed toward adjacent β strands. Rotation of this region in 3 dimensions detected a deep hydrophobic groove within the structure. Energy

calculations and docking procedures indicate that this groove could easily accommodate a straight chain aliphatic ligand (e.g., an FFA) 27 carbons long, with a cylindrical volume of 350 Å³; it can maximally accommodate a 9 residue hydrophobic polyalanine sheet with a volume of 500 Å³. The hydrophobic groove in mAspAT is thus similar in volume to the FFA binding sites of albumin and the cytosolic FABPs.

In further studies FABPpm was delipidated by Folch extraction and the extracts analyzed by GC/MS. Despite FABPpm purification under conditions likely to release bound ligands, endogenous C₁₆ and C₁₈ FFA equivalent to 3% of the FFA binding sites were found in the extracts.

Conclusions: Consistent with its proposed role in FFA uptake, mAspAT has a previously unrecognized hydrophobic groove of suitable size to be an FFA binding site.

Molecular Medicine

MM1. Localization of Functionally Active Tissue Factor in Tissues. Singanallore V Thiruvikraman, John Roboz, Arabinda Guha, Yale Nemerson, and John T Fallon. Divisions of Molecular Medicine, Neoplastic Diseases, and Cardiology, and Departments of Pathology, Biochemistry and Medicine, Mount Sinai Medical Center, New York, NY.

Statement of the Problem: Tissue factor (TF), a transmembrane protein found on the plasma membranes of many cell types, forms a high affinity complex with coagulation factor VII/VIIa (FVII/FVIIa) and thereby initiates blood coagulation via activation factors IX and X.

Methods: To investigate TF activity in tissues, we developed a novel technique for the *in situ* detection of functionally active TF by using digoxigenin-labeled human recombinant factor VIIa (DigFVIIa) and factor X (DigFX). The DigFVIIa was prepared by reacting human recombinant FVIIa with 50-fold molar excess of digoxigenin-3-O-methylcarbonyl-ε-aminocaproic acid-N-hydroxysuccinimide ester (Dig ester).

Results: The DigFVIIa was found to be similar to FVIIa in FX activation. Using 5 pM TF, and 150 nM FX, the K_{d,app} of both species was <6 pM. The catalytic activity of DigFVIIa when extrapolated to infinite concentration was lower than FVIIa (0.79 nM min⁻¹ vs. 1.24 nM min⁻¹ for FVIIa).

DigFX was similarly prepared with 15-fold molar excess of the Dig ester. DigFX showed comparable activity to FX as a substrate for TF-FVIIa: the K_m of Dig FX was 22 nM and the V_{max} 0.83 nM min⁻¹ and for FX the K_m was 19 nM and the V_{max} was 1.45 nM min⁻¹. A novel approach to the characterization of the digoxigenin labeled factors, using electrospray mass spectrometry to determine the masses of the derivatives in their intact forms, revealed the uptake of 26–50 Dig residues by FVIIa and 3–11 residues by FX, yielding molecular weights in the 65–79 Kda and 59–64 Kda ranges.

Conclusions: Our results indicate that the labeling, with retention of functional activity, was more efficient for FVIIa than for FX. The prepared DigFVIIa and DigFX were used to localize functionally active TF in histological sections of formalin fixed, paraffin-embedded human tissues.

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MM2. The Activity of Tissue Factor-Factor VIIa Incorporated into Vesicles Is Controlled by Short-Range Interactions and Tissue Factor Clustering. Harry A. M. Andree¹, Peter L. A. Giesen¹, R. Gentry³, and Yale Nemerson^{1,2}. Departments of Medicine¹ and Biochemistry² and Mount Sinai School of Medicine (CUNY), New York, NY, USA, and Dept. of Mathematics and Statistics³, University of Guelph, Guelph, Ontario, Canada.

Statement of the Problem: Phospholipid surfaces play an important role in blood coagulation. For example, the activation of factor X by tissue factor (TF)-factor VIIa is greatly enhanced by anionic phospholipids. The function of the phospholipid surface has been a matter of discussion. One hypothesis is that the surface enhances the reaction rate by concentrating the substrate followed by lateral diffusion across the surface to the enzyme, the so-called membrane bound substrate model. If diffusion in this model occurs over long distances (>50 nm), then the K_m is a direct function of the phospholipid area around the enzyme. An alternative explanation for the enhancement of catalysis is that binding orients the substrate via restricted rotational diffusion.

Results: We find no effect of vesicle size (30–150 nm diameter) on the K_{m,app}, all done with 16 factor X concentrations (K_{m,app} = 8–10 nM). This K_{m,app} can be explained by assuming that each molecule within a minimal capture radius of 2 nm from the enzyme is converted with 100% efficiency. With a lower efficiency, the upper limit of the capture radius, 30 nm, is given by the size of the smallest vesicles used. These data indicate that the size of the phospholipid area around the enzyme is of relatively low importance.

This contrasts with our observation that the K_{m,app} is dependent on the enzyme density of the vesicles: K_{m,app} was 8.8 ± 0.7 nM (S.E., n = 10) for 1 TF/vesicle and 24 ± 2 nM (S.E., n = 7) for 6.7 TF/vesicle. This apparent discrepancy can be explained by enzyme-enzyme interactions with overlapping radii of capture. This hypothesis was supported by the finding that most of the TF-molecules could be cross-linked using a reagent with a spacer arm length of 1.14 nm. The clustering of membrane bound molecules is in accord with our two-dimensional Monte-Carlo simulations which show that with 1% surface coverage and k_{off} = 4000 s⁻¹ about 71% of the molecules appear in clusters.

Conclusions: We conclude that predominantly molecules in close proximity to the enzyme are converted. In other words, long-range lateral diffusion does not play a major role.

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MM3. Anionic Phospholipids and Prothrombin Transport Are Key Regulators of Thrombin Generation in Flowing Plasma. Harry A. M. Andree¹, Peter L. A. Giesen¹, R. Gentry³, and Yale Nemerson^{1,2}. Departments of Medicine¹ and Biochemistry² and Mount Sinai School of Medicine (CUNY), New York, NY, USA, and Dept. of Mathematics and Statistics³, University of Guelph, Guelph, Ontario, Canada.

Statement of the Problem: The determination of thrombin generation rates in plasma has provided valuable insight into the biochemistry of coagulation reactions, which cannot be easily predicted from purified systems. However, limited attention has been given to coagulation kinetics in flowing plasma. To approach more physiological conditions, we have investigated the effects of flow on thrombin generation in human plasma.

Methods: Glass capillaries were coated with phospholipid bilayers containing the transmembrane protein, tissue factor (TF). The capillaries were perfused with defibrinated plasma reconstituted with calcium in the automated continuous flow reactor system at 37°C. Thrombin was measured in the effluent which was collected into ELISA plates containing EDTA and chromogenic substrate (S-2238).

Results: For tubes coated with 5% PS, 95% PC and high density TF (52 fmoles/cm²), steady-state thrombin production was observed in less than two minutes at a level of 6.5 ± 0.7 pmoles/min/cm² (n = 6) at a shear rate of 300 sec⁻¹. This level of thrombin production (~200nM) corresponds to about 15% of the normal plasma prothrombin concentration (1.4μM) and is in close agreement with the mass transport rate of prothrombin to the wall of the capillary. This strongly suggests that thrombin production in flowing plasma is limited by the delivery of prothrombin to the phospholipid surface.

Transport rate limited conversion was confirmed with prothrombin deficient plasma where exogenous prothrombin was added. Thrombin production was linear with prothrombin concentration from 0 to 2 μM. The effect of TF surface density on the steady-state thrombin production revealed half maximal thrombin generation at 2.7 fmoles TF/cm², which represents only 0.05% of the total surface area of the tube covered with enzyme. At TF surface densities greater than 20

fmoles/cm², thrombin production became insensitive to enzyme density. However, experiments done with pure PC membranes containing TF showed little detectable thrombin production, even at high TF surface densities. Factor Xa production was also markedly reduced and amounted to less than 15% of the direct activation of factor X by TF:VIIa observed in the purified system. We have demonstrated that VII activation and TF:VIIa complex formation are not limiting factors in plasma and that tissue factor pathway inhibitor (TFPI) is the major source of inhibition, responsible for more than 50% inhibition of TF in the tube. AT-III and protein S were found to have minimal inhibitory effect on factor Xa.

Conclusions: This work highlights two important concepts in the regulation of coagulation: convective transport of substrates to the site of injury and the necessity of anionic phospholipids at the site of injury for initiation and sustained hemostasis.

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Neoplastic Diseases

ND1. Role of the Tumor Suppressor Protein p53 in a G2 Checkpoint. Jessica Cohen and James J. Manfredi. Division of Neoplastic Diseases, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: The tumor suppressor protein p53 is a transcription factor which functions in the cellular response to DNA damage. DNA damage induced by a variety of agents, including ionizing radiation, ultraviolet light, or particular chemotherapeutic drugs, causes p53 levels to increase. This increase in p53 expression results in activation of several target genes, notably the cyclin-dependent kinase inhibitor p21. Studies to date have produced consistent results demonstrating that the negative growth effect of p53 leads to a block at the G₁/S border prior to the onset of DNA synthesis.

Methods: Treatment of two cell lines, the mouse mammary epithelial line C127I and the human breast carcinoma line MCF7, with the dye Hoechst 33342 resulted in an arrest in the G2 phase of the cell cycle as determined by double-labeling the cells with propidium iodide and bromodeoxyuridine and subjecting them to flow cytometry. Immunoblotting of cell extracts with an anti-p53 antibody demonstrated that the level of p53 in these Hoechst-treated cells was dramatically increased. In contrast, treatment of the cells with other agents which induce cell cycle arrest at other points in the cell cycle, such as aphidicolin or hydroxyurea, did not cause an increase in the level of expression of p53. Nuclear extracts of MCF7 cells after treatment with Hoechst dye were prepared and the ability of the p53 in these extracts to bind to DNA was examined by electrophoretic mobility shift assay (EMSA).

Results: Ultraviolet light (UV) treatment of MCF7 cells induced an increase in p53 levels and nuclear extracts from UV-treated cells demonstrate a shifted complex by EMSA which contained p53 as seen by supershifting with a p53-specific antibody. Nuclear extracts from Hoechst-treated cells produced a mobility shift comparable to that seen in extracts from UV-treated cells using a double-stranded oligonucleotide probe containing a high affinity binding site for p53. That the shifted complex contained p53 was demonstrated by a supershift of this complex after addition of a p53-specific antibody, PAb 1801.

Treatment of a p53-negative cell line, Saos-2, with Hoechst 33342 did not cause cell cycle arrest. This latter result suggests that p53 may be necessary for the G2 arrest seen in MCF7 and C127I cells.

Consistent with these observations are studies utilizing rat embryo fibroblasts which overexpress the temperature sensitive p53^{val132}. At 37°C, p53^{val132} acts like mutant p53, whereas at 32°C p53^{val132} behaves like wild-type p53 and induces growth arrest. We have screened a number of different clones expressing p53^{val132}, the major-

ity of which show a strong G1 arrest upon incubation at 32°C. Two cell lines, however, have been identified which arrest at 32°C with half of the cells in the G1 phase and half of the cells in the G2 phase of the cell cycle.

Conclusions: Taken together, all of these results suggest a role for the growth-suppressing activity of p53 in a G2 checkpoint as well as in arrest in the G1 phase of the cell cycle.

ND4. Cellular Factor Stimulates the Ability of p53 to Bind to DNA in a Sequence-Specific Manner. Lois Resnick-Silverman, Sungmee Kim, and James J. Manfredi. Division of Neoplastic Diseases, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: As the DNA binding activity of p53 is essential for the ability of p53 to function as a tumor suppressor, cellular mechanisms that prevent p53 from binding to its cognate DNA site should represent mechanisms of oncogenesis.

Methods: With this in mind, a biochemical fractionation approach was undertaken to identify cellular factors that regulate the ability of p53 to bind to DNA in a sequence-specific manner. The initial approach was to screen extracts of p53-negative cell lines to avoid difficulties in interpreting results due to the presence of p53 in the extracts. These extracts would be examined for activities which affect the ability of purified p53 to bind to DNA in a sequence-specific manner as assayed by an electrophoretic mobility shift assay (EMSA). Addition of a nuclear extract of the human osteosarcoma cell line Saos-2 to human p53 purified from baculovirus-infected insect cells resulted in a significant enhancement (20-fold) of the ability of the purified p53 to interact with DNA.

Results: The nuclear extract did not cause an alteration in the apparent size of the binding complex, but rather increased the amount of shifted probe. Heat treatment of the nuclear extract completely abolished the ability of the extract to stimulate the binding of p53 to DNA. Saos-2 nuclear extract stimulated the ability of p53 to bind to both a DNA sequence that is a perfect consensus binding site or to a DNA binding site from a relevant cellular target, the p21^{CIP1} promoter. The enhanced shift seen in the presence of Saos-2 nuclear extract was efficiently supershifted by incubation with an anti-p53 monoclonal antibody.

The enhancing activity, which we call p53EF, was found in both cytosolic and nuclear fractions. The activity was found in a variety of human cell lines, including both tumorigenic (MCF7) and nontumorigenic (Saos-2) tumor cells, leukemic (HL-60), immortalized (MCF10F), and primary (WI38) cells. p53EF has been purified by standard biochemical methods.

The behavior of p53EF is consistent with it being protein in nature with an apparent native molecular weight of 80 kd. Addition of ATP does not affect the ability of p53EF to stimulate the DNA binding activity of p53. Since it is unlikely that any endogenous ATP would co-purify through three columns and a dialysis step, it is unlikely that p53EF requires ATP for its activity, making it unlikely that p53EF represents a kinase activity or a chaperonin activity similar to the bacterial dnaK protein.

There are several potential mechanisms by which p53EF may operate, including the modification of p53 itself, the contribution of a binding component to the p53 binding complex, or the release of p53 from binding to an inhibitor. Studies to distinguish these various mechanisms are underway.

Conclusions: Thus, a cellular activity has been identified which stimulates the ability of p53 to bind to DNA. As the ability to bind to DNA is critical for the tumor suppressor activity of p53, elucidation of the mechanism underlying p53EF may reveal an important new target in oncogenesis.

ND5. Multiple Cellular Mechanisms to Overcome p53-Induced Growth Arrest. Lois Resnick-Silverman and James J. Manfredi. Division of Neoplastic Diseases, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: To establish cell lines which are resistant to growth arrest by p53.

Methods: Rat embryo fibroblasts that overexpress a temperature-sensitive p53 were employed. At 37°C, the temperature-sensitive p53^{val132} acts like mutant p53, whereas at 32°C, p53^{val132} behaves like wild-type p53 and induces growth arrest.

Results: Fifteen different cell lines expressing the temperature-sensitive p53^{val132} have been established and these were examined for their ability to arrest growth at 32°C as seen by flow cytometry. Ten of the lines showed an accumulation of cells in the G₁ phase; four cell lines did not. Pulse-labeling with bromodeoxyuridine confirmed that these cell lines continue to synthesize DNA at 32°C. This inability to arrest growth is not due to insufficient expression of p53, as the cell lines that fail to arrest growth at 32°C all have levels of p53 greater than that seen in a cell line which expresses a low level of p53 and still arrests growth at 32°C.

These results suggest that these four lines have developed mechanisms for inactivating the growth-suppressing activity of p53, and therefore such lines would serve as good model systems for identifying novel mechanisms for regulating p53.

Two of these cell lines have been characterized. Immunofluorescence and biochemical fractionation were performed to determine the subcellular localization of the p53. The ability of p53 to bind to DNA was examined by electrophoretic mobility shift assay using nuclear extracts as a source for p53. The ability to supershift gel shifts with p53 specific antibodies was used to identify shifted complexes which contain p53. Immunoblotting of whole cell extracts was used to determine whether there was an elevation of expression of particular p53 target genes, including p21^{CIP1} and mdm2. Experiments such as these demonstrated that in one line (VS4-6), the p53 behaved as wild-type, in that it was localized to the nucleus, bound DNA in a sequence-specific manner, and could activate transcription of target genes. This line also expresses a novel p53 binding protein (see below). In a second line (VS2-4), the p53 was found to be nuclear; however, it appeared to be defective in its sequence-specific DNA binding activity. Thus, these rat cell lines demonstrated multiple mechanisms to overcome p53-dependent growth arrest. The cell line VS4-6 expresses a readily detectable p53 binding protein with an apparent molecular weight of 140 kd. p140 is co-immunoprecipitated by different monoclonal antibodies which reacts with a variety of epitopes on p53. [³²P] labeling experiments demonstrated that p140 is a phosphoprotein.

Conclusions: These results suggest that p140 is a novel p53-binding protein that may represent one of the mechanisms by which cells become resistant to p53-induced growth arrest.

ND6. Cryoablation—A New Approach for Unresectable Liver Tumors. Michail Shafir MD, Robert Shapiro MD, Max Sung MD, Richard Warner MD, Arthur Siclar MD, Adam Klipfel RS. Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: Nonresectable liver malignancies, including gastrointestinal metastases are lethal in a vast majority of patients.

Methods: Cryodestruction of such tumors was performed in 39 patients with a liquid nitrogen probe, delivering tumoricidal temperature of -196°C, under intraoperative ultrasound guidance.

Results: Histology: 25 colorectal metastases, 3 gastric metastases, 4 hepatocellular carcinomas, 6 carcinoids, and 1 gastrinoma. All completely treated patients are alive with mean follow-up of 14 months. Five patients with incomplete cryoablation died between 3 and 9 months. Thirteen have recurrent disease (28%) and 20 are NED (51%). There were no operative mortalities. Complications (9%): 1 coagulopathy, 1 transient renal failure, one diaphragmatic and skin cryoinjury. Postoperative thrombocytopenia and elevation of liver function tests and serum tumor markers were observed, witnessing intensity of tissue destruction. All patients received postoperative chemotherapy.

Conclusions: Cryoablation appears to be an active and safe treatment for advanced malignancies. Further multimodality studies are indicated.

ND7. Cytoplasmic Localization of p53 in Breast Carcinoma Cell Lines Does Not Block p53-Dependent G₁ Arrest in Response to DNA Damage. Hsin-yi Tang, Samuel Waxman, and James J. Manfredi. Division of Neoplastic Diseases, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: In addition to direct genetic alteration of the tumor suppressor protein p53, nuclear exclusion of wild-type p53 has been suggested as a mechanism for functional inactivation of p53 in a subset of human breast tumors.

Methods: To investigate this notion, we have identified two breast carcinoma cell lines (MCF7 and ZR-75-1) which express a wild-type p53 that is localized to the cytoplasm.

Results: In spite of this cytoplasmic localization of p53 prior to DNA damage, these cell lines were capable of responding to DNA damage in a p53-dependent manner. The level of p53 expression increased in response to ultraviolet light (UV), ionizing radiation, or treatment with adriamycin. Biochemical fractionation and immunocytochemical staining demonstrated that the level of p53 increased in both the nuclear and cytoplasmic compartments. The p53 in both compartments after DNA damage was capable of binding to DNA as determined by both electrophoretic mobility shift assay (EMSA) and an immunoprecipitation assay. After DNA damage, the levels of mdm2 and p21^{CIP1} protein increased as detected by immunoblotting, consistent with the ability of p53 to transcriptionally activate its target genes. Finally, flow cytometric analysis using dual-labeling with propidium iodide and bromodeoxyuridine showed that both cell lines were growth-arrested in response to treatment with these DNA damaging agents.

Our results show that cell lines expressing a cytoplasmically localized p53 can still function in response to DNA damage and cytoplasmic localization per se does not rule out a p53-dependent response to treatment with DNA damaging agents. In contrast to MCF7 and ZR75-1, three other human cell lines expressing wild-type p53 show exclusively nuclear localization both before and after DNA damage. These lines include the nontransformed, nonimmortalized WI38 (lung fibroblasts), the nontransformed but immortalized MCF10F (breast epithelial cells), and the transformed and immortalized U-87 MG (glioblastoma cells). MCF10F cells were released from serum starvation and followed through the cell cycle by flow cytometry and immunocytochemical staining of p53.

Conclusions: These studies demonstrated that the wild-type p53 in MCF10F cells was transiently localized to the cytoplasm during the S phase of the cell cycle. These data are consistent with the notion that both MCF7 and ZR-75-1 cells express a cytoplasmic localization mechanism for p53 which is no longer under normal cell cycle control. The cytoplasmic p53 in untreated cells was capable of binding to DNA as determined by EMSA and immunoprecipitation assays. Since the level of wild-type p53 that is expressed in these cells is not compatible with normal cell growth, and since this p53 retains the ability to bind DNA, cytoplasmic localization of this wild-type p53 may be important for the continued proliferation of these cells.

ND9. Detection of Circulating Metastatic Tumor Cells in Patients with Advanced Prostate Cancer by PSA and PSM RT-PCR. W. Tao, N. Stone, I. Esseesse,* S. Waxman, L. Ossowski, A. C. Ferrari. Division of Neoplastic Diseases and Dept. of Urology, The Mount Sinai Hospital, and *Hematology/Oncology Service, Bronx VA Medical Center, New York.

Statement of the Problem: Prostate cancer progression is biologically defined by the transition from an androgen-dependent to an androgen-independent state. Clinically, this correlates with initial response and subsequent failure to respond to hormonal manipulation. When patients are deprived of androgens, levels of serum PSA decrease as a result of a reduction in cancer cell number due to apoptosis and to inhibition of PSA expression. PSM is prostate-specific integral membrane glycoprotein, which, in contrast to PSA, is down-regulated by androgens. Therefore, PSM may help to identify prostatic cells that stopped expressing PSA due to hormonal ablative therapy as well as anaplastic prostatic tumor cells that lose PSA expression.

Methods: To assess the presence of circulating metastatic tumor

cells, we have established a nested RT-PCR assay to detect PSA and PSM mRNA expression from total mRNA extracted from peripheral blood mononuclear cells (PMN). The sensitivity of the assay determined by cell dilution experiments of LNCaP cells with normal female PMNs is ≥ 1 tumor cell in 10^6 but < 1 tumor cell in 10^7 PMNs.

Results: We processed 19 peripheral blood samples from patients with advanced prostate cancer receiving hormonal therapy. Two cases were PSA RT-PCR positive after 50 cycles of amplification with the external primers only; 5 additional cases became positive after 30 cycles with the nested primers. Seven PSM RT-PCR positive cases became detectable only after 30 cycles with the nested primers. PSA/PSM RT-PCR were positive in 78% of patients with refractory disease or advanced untreated prostate cancer. In patients on hormonal therapy, some of whom showed negative or low serum levels of PSA, RT-PCR was positive in only 30%.

Conclusions: We have established a nested PSA and PSM RT-PCR assay that is specific, sensitive, and reproducible as a tool for detecting circulating metastatic tumor cells. The sensitivity of the assay (one tumor cell in more than 10^6 PMNs) is equal to or higher than what has been described in the literature. We are currently using this assay to evaluate the effect of hormonal ablation and Isotretinoin on circulating metastatic tumor cells. We plan to extend this assay to evaluate the peripheral blood and lymph nodes of patients with clinically localized disease before definitive treatment.

Pulmonary

P2. Regulation of Connexin43 Expression in Rat Aortic Smooth Muscle (RASM). L. R. DePalo, D. C. Spray^{*,} M. Taubman^{*}. Divisions of Pulmonary and Critical Care, Cardiology^{*}, The Mount Sinai Hospital, New York, NY, and ^{*}Department of Neuroscience, Albert Einstein College of Medicine, Bronx, NY.

Statement of the Problem: Gap junctions are channels formed by the apposition of cell membranes containing the hexameric assemblages of structural proteins termed connexins. These channels provide intercellular coupling via the exchange of ions and second messenger molecules. This exchange results in amplification of localized nervous and humoral stimulation, and synchronizes metabolic and electrical activity in these tissues. Intercellular communication via gap junctions is an important mechanism for regulating vascular smooth muscle cell (VSMC) function. Connexin43 is the major gap junctional protein expressed in RASM cells.

Results: We have shown that cultured RASM constitutively express connexin43 and form functional channels (9.43 ± 1.1 nS, SEM, $N = 20$; single channel conductance approximately 90pS) similar to that previously demonstrated in cultured human airway smooth muscle cells. TGF- β and b-FGF are two cytokines known to be important in the regulation of smooth muscle cell differentiation, growth, and cellular response to injury. We show that expression (Northern blot) of connexin43 mRNA in cultured VSMCs can be regulated by TGF- β and b-FGF in a time- and dose-dependent fashion. The magnitude of regulation by cytokine-induced mRNA expression is modest, 2.5-fold, though statistically significant ($p < .05$). Studies in human airway smooth muscle cells have demonstrated that modest increases in mRNA levels result in profound increases in junctional coupling as measured by electrical conductance or intercellular dye transfer.

Finally, using a well-described model of arterial injury (balloon angioplasty), we proceeded to investigate the in vivo regulation of connexin43 expression in vascular tissue. Preliminary studies demonstrate that rat aortic tissue express low levels of connexin43 immunoreactivity. Following arterial injury, in vivo expression of connexin43 immunoreactivity is increased, and this response may be enhanced in response to repeat injury.

Conclusions: We postulate that the cytokine growth factors TGF- β and b-FGF, previously shown to be important in the arterial response

to injury, may play an important regulatory role in gap junction expression. The regulation of intercellular communication in response to injury may influence smooth muscle cell growth, phenotypic expression, and ultimately vasoreactivity. Regulation of this particular response may plan an important role in the final pathophysiological expression of arterial injury.

P4. Hormonal Regulation of MUC4 Gene Expression. E. G. Gollub, H. Waksman, S. Goswami, and Z. Marom. Division of Pulmonary and Critical Care Medicine, Mount Sinai Medical Center, New York, NY.

Statement of the Problem: The human epithelial cell-line (Ishikawa cell) has been used as a model system for studying the regulation of respiratory mucin. Our previous studies on the expression of five mucin genes (MUC1-MUC5c) in Ishikawa cells found that only MUC4 was expressed constitutively and that steady-state levels of MUC4 mRNA could be up-regulated by mucus secretagogues.

Methods: The present study examines the role of hormonal regulation of MUC4 expression by assessing the effects of estrogen and progesterone on MUC4 mRNA levels. The rationale for this approach is based on the following: (1) Ishikawa cells contain receptors for both estrogens and progesterone; (2) there is evidence for an estrogen-induced rhinitis with increased mucus secretion in women using birth control pills as well as in pregnant women; (3) mucus hypersecretion has been treated with steroids as anti-inflammatory agents but a direct transcriptional effect on mucin genes may also be a factor. In the present study, Ishikawa cells were treated with estradiol and progesterone, total RNA was extracted and subjected to Northern and slot blot analyses using a MUC4 oligonucleotide probe to identify and semi-quantify the resulting hybridization bands by densitometric analysis.

Results: The results indicate that addition of 17- β -estradiol to Ishikawa cells causes significant increases in steady-state MUC4 mRNA levels (3-fold) over controls during a 16 hr period; progesterone produced only negligible changes as compared with controls.

Conclusions: These results could indicate transcriptional regulation of MUC4 expression mediated by estradiol via the estrogen receptor or a post-transcriptional effect increasing the stability of MUC4 mRNA. Estrogens have been shown to be involved in both phenomena.

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P5. Inhibition of Phospholipase C Activity by Retinoic Acid in Smooth Muscle Cell Is Mediated via Protein Kinase A. S. K. Goswami, S. Goswami, S. Maayani, and Z. Marom. The Mount Sinai Medical Center, Division of Pulmonary and Critical Care Medicine and Anesthesiology, and Bellevue Hospital, Department of Pathology, New York, NY.

Statement of the Problem: Human respiratory smooth muscle cell (HRSMC) was identified by immunohistochemical staining and the presence of m-RNA encoding α actin and smooth muscle myosin light chain. Bradykinin (BK) and sodium fluoride (NaF) activates phospholipase C (PL-C) in these cells by increasing phosphoinositide (PI) turnover rates.

Methods: [^{3} H] myo-inositol-labeled HRSMC was used to measure inositol phosphates generated by PL-C activation and c-AMP was determined by established method.

Results: BK (10^{-6} – 10^{-4} M) and NaF (1mM–20 mM) enhances PI hydrolysis in a dose-dependent manner. Both effects were blocked by pretreatment of the cells with forskolin (FSK), 10 μ M, and retinoic acid (RA), 1 μ M–30 μ M. RA (1 μ M–30 μ M) increases c-AMP formation (86 ± 5 to 210 ± 8 pmol/mg protein) from the baseline level (38 ± 4 pmol/mg protein). When RA was added along with FSK (10 μ M), the generation of c-AMP was enhanced in a dose-dependent way (982 ± 10 to 2486 ± 28 pmol/mg protein compared to 564 ± 8 pmol/mg protein for FSK alone). The site of activation by NaF is a GTP binding protein.

Conclusions: It is generally believed that a GTP binding protein is

involved in coupling the BK receptor to PL-C, and this GTP binding protein is the target for PKA-mediated phosphorylation and inactivation of PL-C. It is, therefore, reasonable to speculate that both FSK and RA by the generation of c-AMP activates PKA and thereby inhibits BK and NaF induced PI hydrolysis.

Supported by NIH grant HL-37254.

P7. Transthoracic Bioimpedance Analysis in Porcine Endotoxemia. D. Nierman, E. Fein, E. Hannon, J. Mechanick, E. Benjamin. Divisions of Pulmonary/Critical Care, Critical Care, Endocrinology/Metabolism, The Mount Sinai Hospital, New York, NY.

Statement of the Problem: Tissue resistance (R) as measured by bioimpedance analysis (BIA) reflects tissue water content. We have previously shown that right hemithoracic BIA measurements (which measure only the lung and exclude the heart) can reflect increased lung water in cardiogenic pulmonary edema. This study was designed to determine if transthoracic resistance measurements can detect increased lung water in a porcine endotoxemia non-cardiogenic pulmonary edema model.

Methods: Six adult female pigs were sedated, anesthetized, mechanically ventilated and had pulmonary artery catheters placed. Whole body, right transthoracic and in-vitro whole blood (using a conducting cell) resistances in ohms (Ω) were measured using a tetrapolar electrode array and a specially modified Quantum_{dx} System Analyzer (RJL Systems, Inc., Clinton Twp., MI). *E. coli* Lipopolysaccharide B (Difco, Detroit, MI) 150 mcg/kg was given by continuous infusion for one hour.

Results: At one hour, the resistance of the right chest was significantly lower and in vitro blood significantly higher than at baseline. Whole body resistance and PCWP remained unchanged.

	Baseline	1 H	p
SBP (mmHg)	119 $\pm$ 8	116 $\pm$ 15	.515
MPAP (mmHg)	20 $\pm$ 5	37 $\pm$ 7	.009
PCWP (mmHg)	6 $\pm$ 2	6 $\pm$ 2	.883
CO (L/min)	3.94 $\pm$.84	3.08 $\pm$.77	.007
pO ₂ (mmHg)	91 $\pm$ 15	66 $\pm$ 23	.014
Transthoracic resistance (Ω)	13.4 $\pm$ 7.3	10.4 $\pm$ 5.6	.047
Blood resistance (Ω)	211.0 $\pm$ 11.9	307.9 $\pm$ 84.4	.042
Whole body resistance (Ω)	71.5 $\pm$ 16.3	67.5 $\pm$ 14.3	.114
One hour vs baseline by paired t test			

Conclusions: Although there was no change in total body water, BIA was able to detect a shift of water out of the intravascular compartment and into the lung early in endotoxemia. Since pulmonary capillary hydrostatic pressure (PCWP) did not change, this was most likely the result of increased vascular permeability. Transthoracic resistance measurements may provide a way to follow fluid redistribution in sepsis, and to determine when pulmonary capillary permeability and lung water are increased.

P8. Right and Left Ventricular Contractile Reserve in Patients with End-Stage Lung Disease. M. Henzlova*, J. Machac*, J. Diamond*, D. Correa†, M. Courtney†, S. Lansman†, A. Sadeghi†, A. Glass*, G. Schilero†, M. Padilla†. *Department of Cardiology, †Department of Cardiothoracic Surgery and ‡Division of Pulmonary and Critical Care Medicine, Mount Sinai Medical Center, New York, NY.

Statement of the Problem: The severity of cardiac dysfunction influences therapeutic decisions in pts with end-stage lung disease.

Methods: Thirty-nine lung transplant candidates (22M/17F) free of significant epicardial CAD, valvular heart disease, or echocardiographic evidence of an infiltrative process underwent gated blood pool

imaging with right and left ventricular ejection fraction (RVEF, LVEF) determination at rest, and in 19 pts also after up to 40 mcg/kg/min of dobutamine.

Results: Primary disease was COPD in 14 pts, sarcoid in 7, IPF in 12, PPH in 5 and CF in 1. At rest, RVEF was normal ($>40\%$) in 7 pts, mildly to moderately decreased (20–39%) in 26 pts, and severely decreased ($<20\%$) in 6 pts. The corresponding LVEF differed significantly among these groups: 58 $\pm$ 13%, 53 $\pm$ 12% and 40 $\pm$ 10%, respectively ($p = 0.02$). After dobutamine, RVEF increased from 28 $\pm$ 13 to 40 $\pm$ 20% ($p < 0.001$) and LVEF from 54 $\pm$ 14 to 69 $\pm$ 13% ($p < 0.001$) in pts with normal and mildly to moderately decreased RVEF at rest ($N = 15$). RV augmentation was minimal (from 12 $\pm$ 5% to 14 $\pm$ 5%, $p = NS$) in pts with severe RV dysfunction at rest ($N = 4$). However, their LVEF increased significantly (from 41 $\pm$ 8 to 67 $\pm$ 19%, $p = 0.03$).

Conclusions: (1) There is an association between the severity of RV and LV dysfunction at rest. (2) Dobutamine challenge unmasks RV contractile reserve in pts with mild to moderate RV impairment at rest, which appears to be absent in pts with severe RV dysfunction. (3) Significant LV contractile reserve is demonstrable independent of the degree of RV dysfunction. (4) Dobutamine challenge may help to identify pts with reversible LV dysfunction who might otherwise be excluded from lung transplantation.

P9. Determinants of Airway Response to Cotton Bract Extract (CBE). E. Neil Schachter, Eugenia Zuskin, Anatha Reddy, Marion Buck, Nicholas Rienzi, James Godbold, Mount Sinai Medical Center, New York, NY, and Andrija Stampfer School of Public Health, Zagreb, Croatia.

Statement of the Problem: This study examines the role of atopy in determining susceptibility to CBE-induced bronchospasm.

Methods: In 22 healthy nonsmoking subjects (15 male, 7 female, age 31 $\pm$ 1.7 years) we examined indices of atopy: skin testing with ten common allergens and serum IGE. Each subject underwent a screening session at which methacholine challenge was performed. On a separate day each subject was challenged with CBE, and maximal and partial flow volume measurements were performed at 15-minute intervals following challenge for a period of 2 hours.

Results: There were 11 subjects who responded positively to skin testing (+). In this group the average number of reactions to common allergens was 4.3 $\pm$ 0.6. Average serum IGE was 126 $\pm$ 12 for (+) and 64 $\pm$ 7 for skin test negative subjects (–). Baseline lung function studies were within normal limits for the group as a whole, and no significant differences were noted between (+) and (–). The maximal fall in the maximal flow at 40% of vital capacity measured on the partial flow volume curve MEF40%(P) was seen 60 minutes following challenge with CBE. The MEF40%(P) as a percent of baseline at this time point was 56.6 $\pm$ 9.2% for (+) and 86.2 $\pm$ 6.6% for (–) ($p < 0.02$).

Conclusions: We suggest that atopy as measured by skin test reactivity to common allergens predicts responsiveness to CBE.

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P10. Kinetic Characterization of Beta Adrenoreceptor Agonist Induced Relaxation and Rapid, Reversible Desensitization and Resensitization of Airway Smooth Muscle In Vitro. E. Neil Schachter, Daniel E. Wachsmann, and Saul Maayani. Mount Sinai Medical Center, Depts. of Medicine and Anesthesiology, New York, NY.

Statement of the Problem: A kinetic model originally developed in the isolated rabbit aorta (Keitz et al., JPET, 255:650, 1990) was used to study airway responses in guinea pig trachea (GPT).

Methods: Kinetic response parameters in GPT to 0.13 μ M isoproterenol (ISO) were measured in tissues at basal tone and in tissues precontracted with either 1 μ M carbachol (CARB) or 80 mM KCl.

Results: In tissues maintained at basal tone (4–6 g), ISO elicited a monotonic, fast (1–3 min) and reproducible relaxation response,

which was sustained for up to 45 min and was completely reversed by 3 μ M propranolol. By contrast, in tissues precontracted with CARB or KCl, the relaxation was followed by a slower (20–30 min) and partial (~50%) restoration of muscle tone ("fade"). The fade meets criteria for classification as desensitization. In desensitized, washed tissues, a restoration of the relaxation and desensitization responses occurred within 60 min of ISO removal. Epithelium denuded tissues displayed the characteristics of the relaxation and desensitization responses of untreated tissue. Qualitatively similar responses were elicited in isolated human bronchial tissues. In the presence of CARB, the rate constant of relaxation (k_{des} = 0.002 ± 0.001 , n = 44). In the presence of KCl the rate constant of the relaxation was 2–3 times smaller than that observed in the presence of CARB (k_{rel} = 0.004 ± 0.0004 ; n = 16), and the t_{del} was 3–4 times longer (t_{del} = 1006 ± 34 , n = 8).

Conclusions: In summary, the FADE response to ISO of isolated GPT is consistent with homologous desensitization. The partial restoration of muscle tone suggests simultaneous resensitization of GPT.

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P11. Application of the API20E System to Investigate the Etiology of Sarcoidosis. P. Almenoff, M. Lesser, A. Teirstein, A. Johnson, L. Mattman. VA Medical Center, Bronx, NY, The Mount Sinai Hospital, New York, The Hampton VAMC, and Eastern Virginia Medical School, Norfolk, VA, and Wayne State University, Detroit, MI.

Statement of the Problem: Sarcoidosis is a multisystem disorder characterized by the presence of numerous noncaseating granulomas in many organs, including lung, lymph nodes, spleen, liver, and skin. Although pathogenesis of the entity remains unclear despite intensive research efforts for nearly 90 years, cumulative findings strongly implicate mycobacteria as causative factors. In this study we used the analytical profile index (API20E, Plainview, NY) to further investigate the etiology of sarcoidosis.

Methods: The API20E system was designed to perform 23 biochemical tests for the identification of Enterobacteriaceae and other Gram-negative bacilli. We prospectively performed blood cultures of subjects with active untreated pulmonary tuberculosis (n = 15), sarcoidosis (n = 15), and healthy controls (n = 15). Acid-fast cell wall defective forms (CWDF) were recovered from the blood of subjects with tuberculosis and sarcoidosis, but not from healthy controls. Blood cultures of all three groups were inoculated into the API20E system for analysis.

Results: Samples from subjects with tuberculosis and sarcoidosis demonstrated identical patterns of biochemical reactions with the API20E system. These included a positive reaction for arginine dihydrolase (ADH), lysine decarboxylase (LDC), ornithine decarboxylase (ODC), and urease (URE). This combination has never been reported for any established bacterial species. The healthy controls were non-reactive for all of the biochemical tests. No classical bacteria were detected in blood cultures from subjects with tuberculosis, sarcoidosis, or controls.

Conclusions: The finding of identical biochemical reactions by CWDF from patients with sarcoidosis and tuberculosis suggests that mycobacterial organisms are causative factors in the development of sarcoidosis.

P12. Histamine-Induced Airway Hyperactivity in Subjects with Cervical Spinal Cord Injury Is Not Blocked by Pretreatment with Ipratropium Bromide. P. L. Almenoff, E. D. Fein, W. A. Bauman, D. R. Grimm, A. M. Spungen, M. Lesser. Internal Medicine and SCI Services, Veterans Affairs Medical Center, Bronx, NY, and the Departments of Internal Medicine and Rehabilitation Medicine, The Mount Sinai Hospital, New York, NY.

Statement of the Problem: Previously, we reported that subjects with cervical spinal cord injury (C4–8) demonstrate marked bronchial hy-

perresponsiveness when challenged with inhaled methacholine (a cholinergic agonist) or histamine (a nonspecific bronchial irritant). We also found that pretreatment with ipratropium bromide completely blocked the response to methacholine (Chest 1994; 105:1073–76). We attributed bronchial hyperresponsiveness to interruption of sympathetic airway innervation, which originates from the upper six thoracic ganglia, thereby resulting in unopposed parasympathetic activity. This entity was defined as spinal cord airway reactivity syndrome (SCARS). To further explore the mechanism of airway hyperresponsiveness, we performed histamine challenge studies in subjects with chronic cervical spinal cord injury before and after the administration of ipratropium bromide.

Methods: The study group consisted of four subjects (C5–7 lesions), including 1 never-smoker and 3 smokers. The subjects were pretreated on separate days with 4 puffs of ipratropium bromide (72 mcg.) via spacer and then challenged 30 minutes later with nebulized normal saline, followed by progressively increasing concentrations of histamine, until a concentration was reached that caused a 20% fall in FEV1 from baseline (defined as the PC20). In our laboratory a PC20 of <8 mg/mL is considered positive.

Results: Baseline findings of the 4 subjects (mean $\pm$ SD) were FVC% = 57 ± 3.1 , FEV1% = 59 ± 8.1 and FEV1/FVC ratio = 0.80 ± 0.12 . The PC20 of the 4 subjects was 1.70 ± 0.86 before and 3.9 ± 2.25 after pretreatment with ipratropium bromide.

Conclusions: Thus, subjects with spinal cord injury have increased bronchial reactivity to histamine, and the effect is minimally blocked by pretreatment with ipratropium bromide. The findings differ from those of our previous study, which showed that the response to methacholine was completely blocked by pretreatment with ipratropium bromide. These findings suggest that autonomic imbalance in the lung is not the only mechanism responsible for SCARS, and that additional factors may contribute to airway hyperresponsiveness in subjects with cervical spinal cord injury.

P13. A Prospective Randomized Study of Inpatient Intravenous Antibiotics for Community-Acquired Pneumonia: The Optimal Duration of Therapy. RE Siegel, NA Halpern, PL Almenoff, A Lee, R Cashin, JG Green. Bronx VAMC, Castle Point VAMC, Division of Pulmonary and Critical Care Medicine, Mount Sinai Medical Center, New York, NY.

Statement of the Problem: Community-acquired pneumonia (CAP) is responsible for over 1 million hospital admissions/year. To determine if a shortened course of intravenous (IV) antibiotic would result in the same therapeutic outcome when compared to the standard course of 5–7 days of IV therapy, a hospital based, CAP study was conducted.

Methods: Length of stay was determined and a cost analysis was performed. Seventy-three patients with 75 episodes of pneumonia were randomly entered into one of three treatment arms: group I, 2 days of IV and 8 days of oral therapy; group II, 5 days of IV and 5 days of oral therapy; and group III, 10 days of IV therapy. Antibiotics used were cefuroxime (Zinacef) for the IV course and cefuroxime axetil (Ceftin) for the oral course.

Results: Fifty-seven patients were evaluable and no significant difference was found between the groups upon entry. No significant difference was found in the cure rate, duration of fever, leukocytosis, or resolution of chest film abnormalities among the 3 groups. The mean LOS was 6 days in group I, 8 days in group II, and 11 days in group III. Cost analysis revealed a potential cost savings of \$20 million for the VA, all facilities for 1994 and close to \$1 billion for the U.S. private sector for 1992.

Conclusions: Patients hospitalized for CAP of moderate severity can generally be treated with 2 days of IV antibiotics prior to change to oral therapy. This treatment algorithm leads to earlier hospital discharge and substantial cost savings, without a compromise in patient outcome.

Supported by a grant from Glaxo Inc.

Renal

R2. Urea Inhibits NaK2Cl Transport in Human Erythrocytes. J. Lim, C. Gasson, D. M. Kaji. Renal Division, Department of Medicine, V.A. Medical Center, Bronx, NY, and The Mount Sinai Hospital, New York, NY.

Statement of the Problem: Although urea is an accepted marker for the severity of uremia, it is believed that urea itself is nontoxic and does not cause pathophysiologic alterations in uremia. However, urea known to bind to proteins, to perturb their protein structure and folding, and hence to cause a decrease in macromolecular crowding. Recently, it was proposed that cells sense their volume by the degree of macromolecular crowding in the cell. If urea decreases macromolecular crowding, it should result in cell perception that the cell is swollen even as cell volume remains unchanged, and lead to (a) activation of swelling-activated transport pathways and (b) inhibition of shrinkage-activated pathways. Therefore, the present study was designed to examine the effect of urea on NaK2Cl cotransport (a shrinkage-activated cotransport in many cell types) in human erythrocytes.

Methods: K influx was measured with ^{86}Rb in a medium containing NaCl 145 mM, KCl 5 mM, dextrose 5 mM, Tris.MOPS 5 mM, pH 7.4 at 37°C. The bumetanide-sensitive K influx (difference in K influx with and without 2 μM bumetanide) was taken as the measure of NaK2Cl cotransport.

Results: At a concentration of 45 mM (corresponding to blood urea nitrogen concentration of 126 mg/dl), addition of urea to the bath resulted in an inhibition of NaK2Cl cotransport in cells from nine normal subjects ($p < 0.001$ by paired t test), with an average inhibition of $33 \pm 8\%$. Urea inhibited NaK2Cl cotransport in a concentration-dependent fashion, with 50% inhibition at 63 ± 9 mM and near complete inhibition >300 mM. The inhibition was entirely reversible; cells exposed to urea and then washed free of urea showed normal activity of NaK2Cl cotransport. These effects were not due to alterations in cell volume, because cell volume remained unchanged after addition of 500 mM urea. Shrinking and exposure to okadaic acid (a protein phosphatase inhibitor), two maneuvers known to result in phosphorylation of proteins, led to an increase in NaK2Cl cotransport. Cells which were either shrunken, or shrunken and pretreated with okadaic acid, became relatively resistant to the inhibitory effect of subsequent urea addition, suggesting that the action of urea was exerted before the phosphorylation-dephosphorylation step and that urea may exert its action on cotransport by effecting a net dephosphorylation of the cotransporter.

Conclusions: Thus, at relatively low concentrations, similar to those found in uremic subjects, urea inhibits NaK2Cl cotransport in human erythrocytes. Taken together with our finding that urea inhibits NaK2Cl cotransport in medullary thick ascending limb cells (J. Am. Soc. Nephrol. 4:868a, 1993), and alters KCl cotransport in human erythrocytes (Am. J. Physiol. 268: C1018–C1025, 1995), our results suggest that urea may cause widespread alterations of ion transport pathways in uremia. These findings have implications for the pathophysiology of the uremic syndrome.

R3. Transfection Alters Ion Transport in MDCK Cells. D. Kaji, J. Bates, J. D. Goyzueta, K. Prasad, H. Yu, and S. Kumar. Renal Division, Department of Medicine, V.A. Medical Center, Bronx, NY, Mount Sinai School of Medicine, New York, NY, and Warren Medical Research Institute, University of Oklahoma, Oklahoma City, Oklahoma.

Methods: In the course of an investigation into the effect of Tamm-Horsfall protein (THP) on ion transport, we performed stable transfection of THP into MDCK cells using the SV40 or the cytomegalovirus (CMV) promoter. As controls, we transfected MDCK cells with an

“empty” plasmid containing SV40 or CMV promoter but without THP cDNA. In another set of controls, we subjected cells to transfection procedures without DNA (mock transfection).

Results: K influx was not altered in cells subjected to mock transfection procedures without DNA, but both ouabain-sensitive (OS) and ouabain-resistant (OR) components of K influx were diminished in cells transfected with THP-cDNA using either SV40 or CMV promoter. However, K influx was also reduced in cells transfected with a control plasmid containing either the SV40 promoter alone, or the CMV promoter alone, without the THP cDNA. Thus, the transport alterations were caused by transfection and not by THP. The reduction in ouabain-sensitive K influx was accompanied by a proportional reduction in the abundance of Na-K pump units as assessed by ^3H ouabain binding. ^3H Bumetanide binding, a measure of the number of functioning NaK2Cl cotransporter sites, was reduced *pari passu* with the reduction in bumetanide-sensitive K influx.

Conclusions: Thus, the process of transfection alters ion transport in host cells independent of the effects of transfected protein, and this effect is exerted by reducing the number of functioning transporters inserted in the plasma membrane. These results highlight the possibility that alterations in properties of transfected cells may not be solely due to the presence of transfected protein, but the result of some process associated with transfection itself. Without appropriate controls to evaluate this possibility, results of transfection studies are subject to potentially faulty and misleading interpretation.

R4. Urea Inhibits Na-K Pump in Human Erythrocytes. D. Kaji, J. Lim,* C. Gasson,* W. Zaidi.* Renal Section, Department of Medicine, VA Medical Center, Bronx, NY, and Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: Although alterations of Na-K pump have been described in uremia, the role of urea in inhibiting Na-K pump has not been defined. In this study, we examined the effect of urea on Na-K pump.

Methods: K influx was measured by ^{86}Rb in media containing 145 mM NaCl, 5 mM KCl. The ouabain-sensitive (OS) K influx was taken as the measure of Na-K pump activity. The density of pump sites was probed by ^3H ouabain binding.

Results: In 6 different subjects, the addition of urea to the bath inhibited Na-K pump in a concentration-dependent fashion, with 50–75% inhibition at 500 mM, and $15 \pm 5\%$ inhibition at 100 mM. The inhibition was entirely reversible; cells exposed to urea and then washed free of urea showed no difference in OS K influx. An appreciable lag time was noted between the addition of urea and the onset of inhibition, and maximum inhibition was noted only after 90 minutes. Urea decreased the V_{max} for OS K influx but did not alter the affinity for substrates. Urea did not alter ^3H ouabain binding (360 ± 22 vs. 358 ± 33 sites/RBC), suggesting that urea decreases the ion turnover per pump site. Okadaic acid (OA), a protein phosphatase inhibitor, decreased OS K influx, but the effects of OA and urea were not additive, suggesting that urea may act by altering the net phosphorylation of the pump protein or a key regulatory protein.

Conclusions: Urea produces a major, acute, reversible inhibition of Na-K pump activity in human RBCs. The decrease in pump activity is due to a decreased ion turnover per pump site without a change in the pump density. Because many previous abnormalities of Na-K pump were described in washed uremic cells studied in urea-free media, the inhibition of Na-K pump in uremia may be more profound than previously appreciated. It is possible that the abnormalities of ion transport in RBCs may be related to morphological abnormalities of RBCs described in renal failure.

R5. Antibodies to Recombinant Human Erythropoietin Causing Pure Red Cell Aplasia in a Dialysis Patient—A Case Report. S. Prabhakar and T. Muhlfelder. Renal and Hematology Sections, VAMC, Bronx, NY.

Statement of the Problem: Recombinant human erythropoietin (rHuEPO) is believed to be safe and effective in the management of anemia of chronic renal failure and is not specifically known to be immunogenic. We report here a patient who developed pure red cell aplasia (PRCA) as a result of formation of antibodies to rHuEPO.

Case Report: A 67-year-old black male with ESRD due to chronic hypertension began long-term hemodialysis in Sept. 1990. In Oct. 1991 his therapy was changed to CAPD. He was treated with rHuEPO effectively with doses ranging from 100–200 i.u./kg/thrice weekly on HD and weekly on CAPD and maintained a hematocrit in the low to mid thirties.

In the later part of 1992 he developed progressive anemia resistant to maximal doses of rHuEPO and rHuEPO therapy was consequently discontinued. After exclusion of the usual causes of EPO resistance, a bone marrow examination showed a paucity of red cell precursors. Extensive studies to find the cause of PRCA were nonrevealing. Serologic markers for Parvovirus B19 infection including B19DNA and B19IgM were negative in the peripheral blood (courtesy: N. Young, NIH labs). The patient became transfusion dependent, requiring RBC transfusions every 2–3 weeks to maintain a hematocrit of 20%.

Finally we decided to screen his blood for antibodies to rHuEPO, based on anecdotal reports of development of PRCA, mediated by anti-EPO antibodies in animal studies. The patient's serum was tested by radioimmunoprecipitation assay (courtesy: Amgen Inc.) and was first reported to be positive (1:50 dilution) in Mar. 1994. The positivity was confirmed several times in serial samples. Over the next several months, the anemia improved spontaneously associated with a decline in the antibody titre (<1:10 in Mar. 1995). A repeat study of the bone marrow in Oct. 1994 showed the reappearance of erythroid precursors.

Conclusions: To our knowledge this is the first patient reported in the literature to develop anti-rHuEPO antibodies, with a strong causal association with PRCA.

R6. Inhibitory Effects of Urea on Nitric Oxide Synthesis by Macrophage Cells in Culture. Sharma S. Prabhakar and Guillermo A. Zeballos. VAMC, Bronx, NY, and Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: The role of nitric oxide (NO) in the pathogenesis of ischemic and immunologic models of renal injury has been increasingly recognized recently (Klahr et al., *Lab Invest* 1995;72, 1–3). However, the impact of renal failure on the NO synthesis, especially by macrophages, is not clearly understood. Macrophage function is believed to be defective in patients with renal failure, and there is some evidence that nitric oxide (NO) may be the effector molecule of cytotoxic functions of macrophage (Hibbs et al., *Biochem Biophys Res Commun* 1988;157, 87–94). As part of studies to understand the effect of uremia on macrophage function, we examined the effects of urea on the nitric oxide synthesis in macrophages in culture.

Methods: Murine peritoneal derived macrophages (RAW 264.7 cell line) were cultured in RPMI 1640 with L-glutamine (Gibco BRL). Cells were incubated at a concentration (con) of 1×10^5 /well and NO synthesis was induced by lipopolysaccharide (LPS) derived from *E. coli* (serotype 0111:B4) at a con. of 10 µg/mL. A 50 mM solution of urea was then added to the test group and the incubation was continued at 37°C for 18 h. The supernatants were analyzed for NO production by chemiluminescence (Sievers NO analyzer). Nitrite/nitrate content was reduced into NO with a vanadium reducing mixture in a reaction tube on line with analyzer. A standard curve was made in culture media spiked with nitrate.

Results: In the control group (n = 6) the basal NO activity was 645 ± 7 µmoles/L, which increased significantly to 1097 ± 15 µmoles/L with LPS ($p < 0.01$), implying synthesis of inducible isoform of NO synthase. In test samples (n = 6) containing urea, NO activity was 589 ± 2 µmoles/L under basal conditions and significantly lowered to 226 ± 10 µmoles/L with LPS ($p < 0.01$), suggesting that urea inhibited both constitutive and LPS-inducible isoforms of NO synthase activity. All groups were significantly different from each other ($p < 0.01$).

Conclusions: We conclude that urea inhibits NO production by macrophage cells in culture, and that this effect may play an important

role in defective immune response and renal autoregulation observed in renal failure.

R7. Role of NF-κB in the Regulation of the HIV-1 Promoter in a Transgenic Mouse Model. L. A. Bruggeman, P. E. Klotman. Division of Nephrology, Mount Sinai School of Medicine, New York, NY.

Statement of the Problem: The level of HIV-1 transcriptional activity is one of the major determinants of viral replication. Most previous studies evaluating HIV-1 gene expression have used deletional mutagenesis of the LTR with transient transfections of cell lines in vitro. To further these in vitro studies, we are using a recently developed transgenic mouse model of HIV-1 that manifests many syndromes associated with HIV-1 infection, including epidermal proliferation, HIV-associated nephropathy, and pediatric wasting.

Methods: By Northern analysis, expression of the transgene in different tissues is variable from no expression to high levels of expression. Based on these differences, we have used the electrophoretic mobility shift assays (EMSA) to explore in vivo the host transcriptional factors that regulate HIV-1 transcription at the LTR.

Results: EMSAs of the different tissue types have shown a predominant role for NF-κB in the highly expressing tissue similar to that observed in infected T cells. All tissue types had a form of NF-κB in the nucleus which consisted of NFκB1 and RelA or c-Rel identified by supershifts and Western blotting. However, small variations in the molecular weight of these proteins suggests that there may be tissue-specific differences in the NF-κB subunit proteins which may confer specificity to DNA targets. A biotin-streptavidin affinity systems used to purify LTR binding complexes identified tissue-specific differences in the binding of additional host transcriptional proteins including Sp1 and YY1. These studies suggest that tissue-specific differences not only in the NF-κB protein itself, but also in associations with additional transcription factors, contribute to the level of transgene expression.

Conclusions: These studies indicate that while NF-κB is involved in the control of numerous gene in a variety of cell types, it may be possible to identify a highly specific form of NF-κB with activity only on the HIV-1 LTR. This specific NF-κB could be a target for molecular-based therapies to suppress HIV-1 replication without concern for non-specific gene dysregulation and toxicity.

R10. Protein Intake Responds to Increases in Dialysis Delivery in Hemodialysis Patients Already Receiving Adequate Dialysis. Roy G. Marcus, Edith Cohl, and Jaime Uribarri. Renal Division, The Mount Sinai Hospital, New York, NY.

Statement of the Problem: Nutritional status in hemodialysis patients is a strong predictor of morbidity and mortality. Adequate delivery of dialysis is necessary for most hemodialysis patients to maintain their protein nutrition. In general, a single pool Kt/V of 1.2 has been considered adequate hemodialysis. We now report a group of 19 chronic hemodialysis patients who initially had a Kt/V of greater than 1.2.

Methods: The Kt/V in 10 patients (Group 1) was increased from a mean of 1.41 ± 0.11 to 1.85 ± 0.21 primarily by increasing the blood flow and dialysis flow rates. The Kt/V in 9 patients (Group 2) was maintained unchanged at 1.39 ± 0.20 prior to the study and 1.40 ± 0.21 during the study.

Results: After average follow-up of 4 months, the mean nPCR increased in group 1 from a baseline of 1.02 ± 0.20 gm/kg/d to 1.26 ± 0.20 gm/kg/d ($p < 0.01$). The mean nPCR remained unchanged 1.04 ± 0.33 vs. 0.97 ± 0.27 gm/kg/d ($p = 0.70$) in group 2. More importantly, all 5 patients in group 1 with an initial nPCR of <1 gm/kg/d had an increase in their nPCR to >1 gm/kg/d (0.83 ± 0.08 vs. 1.10 ± 0.10 gm/kg/d, $p < 0.02$). All 3 patients in group 2 with an initial nPCR of <1 gm/kg/d had no improvement in their nPCR (0.76 ± 0.06 vs. 0.79 ± 0.09 gm/kg/d, $p = 0.33$).

Conclusions: Our study provides evidence that protein intake in hemodialysis patients will increase with an increase in dialysis deliv-

ered above the level ordinarily considered to be adequate. Most important, this effect is seen in patients who are not eating a significant amount of protein despite receiving a Kt/V of greater than 1.2. We recommend that a trial of increased dialysis be given to patients with inadequate protein intake already receiving a Kt/V of >1.2.

Rheumatology

Rh1. Temporal Association Between Use of Methotrexate (MTX) and Development of Leukemia in Two Patients with Rheumatoid Arthritis (RA). L. D. Kerr, K. Troy, and L. Isola. Divisions of Rheumatology and Hematology, The Mount Sinai Hospital, New York, NY.

Statement of the Problem: Although numerous toxicities have been attributed to the use of low-dose MTX in RA, only a single previous report mentions the development of leukemia (AML) in a patient with RA on MTX.

Case Reports: We are reporting two patients, both with longstanding nodular erosive RA, neither of whom had previously received alkylating agents, who—coincident with the short-term use of MTX—developed acute myelogenous leukemia (AML) and chronic myelogenous leukemia (CML), respectively. In both patients the Philadelphia chromosome was positive. Whether or not these cases represent an adverse effect of MTX treatment has yet to be determined.

Rh2. Anti-inflammatory and Antiviral Effects of Hydroxychloroquine in Two Patients with AIDS and Active Inflammatory Arthritis. M. H. Ornstein and K. Sperber. Divisions of Rheumatology and Clinical Immunology, The Mount Sinai Hospital, New York, NY.

Statement of the Problem: The antimalarial medications hydroxychloroquine (HCQ) and chloroquine (CQ) have been shown to have anti-inflammatory and immunomodulatory properties. They also have novel antiviral effects and can inhibit the replication of several viruses, including retroviruses. Recently HCQ has been shown to inhibit replication of the HIV-1 virus in vitro and in vivo in patients with HIV infection.

Case Reports: We present the cases of two patients with AIDS and severe inflammatory arthritis who were treated with HCQ. HCQ was given in a loading dose of 600 mg daily (with a maintenance dosage calculated to remain below 6.5 mg/kg/day). Initial T-cell subsets were studied in both patients. In one patient, serum and plasma were collected before and one year into HCQ treatment. Assays were performed for T-cell subsets, recoverable HIV-1 RNA, mitogen and antigen specific proliferation, and IL-6 levels. Both patients had a dramatic decrease in their arthritis. Neither patient required immunosuppressive therapy or developed an opportunistic infection. In the patient studied, there was a tenfold decrease in recoverable HIV-1 RNA, improved mitogen and antigen-specific immune responses, and a large decrease in the IL-6 level on HCQ. On cessation of HCQ treatment, both patients had severe exacerbations of their underlying arthritic condition.

Conclusions: Further studies are now required to determine the utility of HCQ in patients with inflammatory arthropathies and AIDS. If HCQ can exert a simultaneous anti-inflammatory and antiviral effect without further suppressing a patient's immune system, it may be the drug of choice for this population of patients.

Rh3. Demonstration of Hepatitis C in Lesions of Cutaneous Vasculitis by PCR. M. H. Ornstein and R. Phelps. Division of Rheumatology and Department of Dermatopathology, The Mount Sinai Hospital, New York, NY.

Statement of the Problem: The hepatitis C virus (HCV) has been implicated in a variety of cutaneous disease, including porphyria cutanea tarda, urticaria, leukocytoclastic vasculitis, lichen planus, and large vessel vasculitis. We studied two patients with known chronic HCV infection who also had circulating cryoglobulins in which HCV was demonstrated by ELISA and RIBA assays. Both patients suffered from intermittent leukocytoclastic vasculitis, proven by biopsy, which remitted during alpha-interferon therapy.

Methods: Skin biopsies during periods of exacerbations were performed with direct immunofluorescence and PCR.

Results: We were able to demonstrate vascular fluorescence for immunoreactants (IgM, C3). In addition, we also detected HCV RNA in the skin biopsies by a novel ligation-dependent polymerase chain reaction (LD-PCR).

Conclusions: We believe that this may represent in situ deposition of hepatitis C-IG immune complexes. This implies that HCV may be directly involved in the pathogenesis of a variety of skin diseases. Such involvement has implications for the diagnosis and treatment of patients, as well as the overall risk to the practitioner who performs such biopsies.

Rh4. Refractory Gout among Heart Transplant Recipients Receiving FK506. M. Wysell, L. D. Kerr, A. Gass. Divisions of Rheumatology and Cardiology, The Mount Sinai Hospital, New York, NY.

Statement of the Problem: Severe refractory polyarticular gout complicating organ transplant maintained by cyclosporine-A has been well described.

Methods: Two patients with well-preserved cardiac function and no sign of rejection after heart transplant but with persistent acute gout were switched from cyclosporine-A to FK506 in order to improve urate clearance.

Results: These two patients were observed to have more frequent gout attacks, continued hyperuricemia, and in one case the rapid development of tophi. This occurred despite treatment of gout and lowering of FK506 levels.

Conclusions: This experience with two patients whose treatment has altered from cyclosporine-A to FK506 solely in order to diminish their acute gout exacerbations demonstrates that despite the theoretical advantage of FK506 on urate clearance, FK506 does not appear to afford an advantage over cyclosporine-A. Severe refractory gout remains an ongoing problem in these patients despite successful transplantation.

Spinal

Sp1. Insulin-Like Growth Factor-I is Related to Fat-Free Mass in Subjects with Spinal Cord Injury. W. Bauman, Y. Zhong, A. Spungen, and R. Pierson. Spinal Cord Damage Research Center, Departments of Medicine and Rehabilitation Medicine, Mount Sinai School of Medicine, Veterans Affairs Medical Center, Bronx, NY, and Body Composition Unit, St. Lukes/Roosevelt Hospital Center, New York, NY.

Statement of the Problem: The secretion of human growth hormone (hGH) to stimulation with IV arginine and basal serum insulin-like growth factor-I (IGF-I) levels in chronic spinal cord injury (SCI) were shown to be decreased compared with nonSCI controls (Bauman et al., *Horm Metab Res*, 1994). Depressed GH/IGF-I levels have been described to have unfavorable effects on body composition. SCI individuals have loss of lean body tissue immediately after paralysis, but studies have not related anabolic hormones with residual lean tissue during the chronic phase. Loss of muscle tissue may be accelerated as

a consequence of reduced IGF-I levels. Here we report on the relationship of IGF-I with lean tissue mass.

Methods: Thirty subjects with SCI (15 with paraplegia and 15 with quadriplegia) were healthy and were not taking any medications which would interfere with hGH release. Fat-free mass (FFM) was determined by 3 independent methods: dual energy x-ray absorptiometry (DXA, Lunar Radiation Corp., Madison, WI), total body water (TBW, dilution of tritiated water), and total body potassium (TBK, 4 Pi counting chamber). Thirty subjects had DXA and TBK, 12 had TBW measurements performed. Serum IGF-I was measured by RIA.

Results: Values are expressed as mean $\pm$ SEM. The mean age of the group was 40 ± 2 y, duration of injury, 10 ± 2 y, height, 179 ± 1 cm, weight, 80.8 ± 2.7 kg, and BMI, 25.2 ± 0.9 kg/m². Data were analyzed by linear regression analyses. Serum IGF-I was significantly predictive of both measures of %FFM (TBW, $r = 0.70$, $p < 0.01$ and DXA, $r = 0.48$, $p = 0.014$) and of the ratio of TBK/FFM_{DXA} (mEq/kg) ($r = 0.53$, $p = 0.003$).

Conclusions: In summary, during chronic SCI, serum IGF-I is associated with %FFM and may play a vital role in reducing secondary loss of lean tissue due to chronic immobilization. Efforts to maintain IGF-I levels in the normal range would be expected to preserve muscle mass and thus improve the quality of life of these individuals. Alternatively, a provocative hypothesis is that lean body tissue may itself have a role in the maintenance of IGF-I levels, possibly by enhanced production.

Sp2. Analysis of Heart Rate Variability in Subjects with Spinal Cord Injury. D. Grimm, R. De Meersman, P. Almenoff, A. Spungen, W. Bauman. The Spinal Cord Damage Research Center and Departments of Medicine and Rehabilitation Medicine, Mount Sinai Medical Center; Spinal Cord Injury and Medical Services, V.A. Medical Center, Bronx, NY.

Statement of the Problem: Heart rate variability (HRV) is a relatively new method of assessing the autonomic nervous system (ANS), and offers a noninvasive technique to analyze autonomic control (sympathetic and parasympathetic) of the cardiovascular system.

Methods: Thirty healthy spinal cord injured (SCI) males and ten nonSCI males participated in this study. The SCI were classified into three groups according to level and degree of completeness: above cervical vertebra seven (C7), complete lesion; above C7, incomplete lesion; and below thoracic vertebra seven with no distinction based on completeness of lesion. Subjects were initially studied in the supine position; then, three standard provocative maneuvers of the ANS were performed. The three provocative maneuvers, head-up, cold pressor test, and isometric test, were administered to augment sympathetic response. Five minutes of data detailing cardiac function were labeled during each test using a Holter monitor. The first 256 successive R-R intervals of data were analyzed, and the HRV power spectrum was computed using a 512 point fast Fourier transform algorithm. Two distinct spectral components were revealed: a low-frequency (LF) component between 0.05 and 0.15 Hz and a high-frequency (HF) component between 0.15 and 0.35 Hz. The HF peak is mediated by parasympathetic pathways, and the LF peak, primarily by sympathetic with some parasympathetic influence. The LF:HF ratio, an estimate of sympathovagal balance, was calculated from the frequency components of each subject. Data from the three provocative maneuvers were grouped into a single composite variable for each spectral component (LF, HF) and for the ratio (LF:HF). ANOVA and contrast coding was performed to determine differences among the four groups. Post hoc analysis was conducted using Scheffe pairwise comparisons ($p < 0.05$), and a Bonferroni adjustment was applied to the nonorthogonal contrast coding, setting the level of significance at $p < 0.016$.

Results: The HF and LF components of HRV for both groups with quadriplegia were significantly different ($p < 0.05$) from those of the nonSCI group for all maneuvers. The group with paraplegia demonstrated significantly lower HF baseline and LF composite levels than the nonSCI controls ($p < 0.05$). Further analysis using nonorthogonal contrast coding demonstrated that both groups with quadriplegia also significantly differ ($p < 0.002$) from the group with paraplegia for both spectral components of baseline and composite variables. No differ-

ences were observed among all groups for the LF:HF ratio, despite a reduction in autonomic innervation to the heart in subjects with SCI.

Conclusions: In summary, the results indicate that in subjects with quadriplegia, sympathetic innervation to the heart is significantly reduced compared to either those with paraplegia or nonSCI controls. We previously observed a significant difference in autonomic innervation to the heart between individuals with complete and incomplete quadriplegia (Grimm et al., *Am J Physiol* 1995); however, the significance of this difference is lost due to the overriding differences between nonSCI subjects and those with quadriplegia. The observation of no significant differences in the LF:HF ratio among groups suggests that the ANS attempts to maintain homeostasis even when one component is severely compromised.

Sp3. In Human Platelets Insulin ADP-Ribosylates G α and Upregulates Prostaglandin (PG)_{I₂}/E₁ Receptor Numbers. N. Kahn, W. Bauman, A. Sinha. Division of Medicine, Mount Sinai School of Medicine, New York, NY, and Spinal Cord Damage Research, Veterans Affairs Medical Center, Bronx, NY.

Statement of the Problem: Physiologic amounts of insulin increase both the PGI₂/E₁ receptor numbers and the sensitivity of human platelets to the inhibitory effect of the prostanoid through the increased stimulation of adenylate cyclase (Kahn & Sinha, *J Biol Chem* 265: 4976, 1990). This effect of insulin was found to be mimicked by pertussis toxin (PT) and its A-protomer (subunit). Since PT is known to ADP-ribosylate G α , experiments were performed to determine whether the hormonal effect was mediated through a similar mechanism.

Methods: Incubation of platelets with 1.4 nM ¹²⁵I-insulin at 23°C for increasing time periods resulted in increased binding of the radioligand as determined by membrane (GF/C) filtration. The equilibrium binding was achieved in ~150 min. The increased insulin binding simultaneously effected the increased ADP-ribosylation of G α in a dose-dependent manner reaching maximal level also at ~150 min. The insulin induced ADP-ribosylation of G α was determined by autoradiography using ³²P-NAD as well as by immunoblotting.

Results: The increase of modified G α was directly related to the increase of PGI₂/E₁ receptor numbers in platelets. On the other hand, insulin-treated platelets, when resuspended in hormone-free media, showed similar kinetics of de-ADP-ribosylation of G α and the decrease of PGI₂/E₁ receptor numbers.

Conclusions: These results suggest that the degree of ADP-ribosylation by the hormone is functionally related to the expression of PGI₂/E₁ receptors on the platelet surface by insulin.

Sp4. Thromboxane A₂ Levels Are Not Elevated in Subjects with Chronic Spinal Cord Injury. N. Kahn, R. Zhang, W. Bauman, A. Sinha. Division of Medicine, Mount Sinai School of Medicine, New York, NY, and Spinal Cord Damage Research, Veterans Affairs Medical Center, Bronx, NY.

Statement of the Problem: Subjects with spinal cord injury (SCI) are more prone to develop premature coronary artery disease (CAD). Aggregation of blood platelets plays a vital role in the development of CAD. Thromboxane A₂ (TXA₂), produced from arachidonic acid via the cyclo-oxygenase pathway, is a potent platelet aggregating agent and a vasoconstrictor, causing contraction of a wide variety of vascular and smooth muscles. TXA₂ is synthesized during platelet aggregation. An important mediator of secondary aggregation and release reaction, TXA₂ may contribute to the development of CAD in those with SCI.

Methods: We assessed the biosynthesis of TXA₂ as an index of platelet activation in the plasma of subjects with chronic SCI. TXB₂ was assayed by radioimmunoassay.

Results: No statistically significant difference was observed in the TXA₂ levels in those with chronic SCI when compared with nonSCI controls (11 ± 1.38 vs. 8 ± 0.66 pg/0.1 mL, respectively). Elevated levels of TXA₂ in plasma in other vascular diseases has been correlated

with increased sensitivity of the platelets to aggregation by agonists. However, the platelets from subjects with SCI were not more sensitive to these agonists, including ADP, *l*-epinephrine, collagen or thrombin ($3.5 \pm 1.1 \mu\text{M}$; $2.2 \pm 1.5 \mu\text{M}$; $2.0 \pm 0.1 \mu\text{g/mL}$; 0.2 ± 0.05 unit, respectively). Furthermore, an increased TXA_2 level would have resulted in the inhibition of platelet adenylate cyclase, resulting in a decrease in platelet cyclic AMP level. On the contrary, there was no significant difference in the cyclic AMP level in the two groups (26.89 ± 8.21 vs. $20.25 \pm 4.10 \text{ pmol}/10^8$ cells). Although plasma TXA_2 measured higher in some subjects with SCI, levels were still within the normal range (10 to $30 \text{ pg}/0.1 \text{ mL}$; Fitzgerald GA, Healy C, Daugherty A, Fed Proc 46: 154, 1987).

Conclusions: These results suggest that TXA_2 levels are not elevated in subjects with chronic SCI and probably do not contribute to the pathogenesis of CAD.

Sp5. Insulin Restores the Down-Regulation of High-Affinity Prostacyclin Receptors and Loss of Prostacyclin-Induced Inhibition of Platelet-Stimulated Thrombin Generation. N. Kahn, W. Bauman, A. Sinha. Division of Medicine, Mount Sinai School of Medicine, New York, NY, and Spinal Cord Damage Research, Veterans Affairs Medical Center, Bronx, NY.

Statement of the Problem: Individuals with chronic spinal cord injury (SCI) have an increased incidence of premature coronary artery disease (CAD). Hyperaggregation of platelets is known to play a vital role in the pathophysiology of CAD. Also, the prostaglandin (PG)-induced synthesis of cyclic MAP in CAD is decreased due to the impairment of PGE_1/I_2 receptor activity in platelets. Since the incidence of CAD is increased in those with SCI, we investigated the role of PGI_2 in the inhibition of platelet aggregation in relation to prostanoid receptor function and platelet-stimulated thrombin generation.

Methods: In washed platelets the binding of PGI_2 , using $^3\text{H-PGE}_1$ as a probe, was studied (Kahn and Sinha, J Biol Chem 265:4976, 1990). The rate of thrombin generation was measured by Hoggie's method.

Results: In SCI platelets the binding of PGE_1 was $<50\%$ of controls. However, there was no significant difference in the increase of cyclic AMP levels in the two groups (26.23 ± 8.21 vs. $20.25 \pm 4.1 \text{ pmol}/10^8$ cells). Scatchard plot showed that the decreased PGE_1 binding in SCI platelets was due to a decrease in the high-affinity receptor numbers (48 ± 11 sites/cell) when compared with control (172 ± 23 sites/cell). Furthermore, unlike in nonSCI platelets, PGI_2 failed to reduce the rate of thrombin generation in SCI platelets. Since insulin up-regulates high and low affinity PGE_1/I_2 receptors in platelets (Kahn, 1990), treatment of SCI platelets with insulin ($200 \mu\text{Units/mL}$) restored both the number of high-affinity prostanoid receptors (142 ± 36 sites/cell) and the PGI_2 -induced inhibition of platelet-stimulated thrombin generation.

Conclusions: These results suggest that the loss of high-affinity PGI_2 receptors in SCI platelets may contribute to the increased incidence of CAD in SCI. The inhibition of platelet aggregation and platelet-stimulated thrombin generation are under separate regulatory control mechanisms.

Sp6. Increased Energy Needs in Patients with Quadriplegia and Pressure Sores. M. Liu, A. Spungen, W. Bauman. The Spinal Cord Damage Research Center and Departments of Medicine and Rehabilitation Medicine, Mount Sinai Medical Center, New York, NY, Spinal Cord Injury and Medical Services, Veterans Affairs Medical Center, Bronx, NY.

Statement of the Problem: Health individuals with quadriplegia generally have a reduced metabolic rate. The development of pressure sores (PS) in individuals with quadriplegia is more prevalent and may affect the metabolic rate. We have investigated the relative energy expenditure in individuals with quadriplegia with and without PS and in healthy ambulatory subjects.

Methods: Resting energy expenditure (REE) was measured by indirect calorimetry. REE was performed at least two hours postprandial after a 30-minute stabilization period in an upright position. Forty-eight subjects were studied. Sixteen subjects were grouped in each of the following categories: quadriplegia with pressure sores (PS-QUAD), quadriplegia without pressure sores (NPS-QUAD), and able-bodied subjects (CONTROL). Analysis of variance was performed using the Scheffe's F ratio for all possible pairwise comparisons.

Results: All results are reported as mean $\pm$ SEM. There were no significant differences among the groups for age, height, weight, or body surface area (BSA). Subjects in the PS-QUAD and CONTROL group had a significantly higher REE than the NPS-QUAD group (1775 ± 74.38 and 1847 ± 67.15 vs. $1538 \pm 66.27 \text{ kcal/day}$, respectively, $p < 0.05$). The percentage of predicted REE (based on Harris-Benedict equation) was significantly higher in both the PS-QUAD group and CONTROL group than in the NPS-QUAD group (104 ± 3.78 and 104 ± 1.08 vs. $89 \pm 2.61\%$, respectively, $p < 0.05$). REE/kg was significantly higher in the PS-QUAD group than in the NPS-QUAD group (24 ± 1.11 vs. $21 \pm 0.83 \text{ kcal/kg}$, respectively, $p < 0.05$). REE/BSA was significantly higher in both the PS-QUAD and CONTROL groups than in the NPS-QUAD group (928 ± 27.64 and 939 ± 17.69 vs. $801 \pm 26.14 \text{ kcal/m}^2$, respectively, $p < 0.05$). Thus, pairwise comparisons revealed PS-QUAD to be significantly higher than NPS-QUAD for energy expenditure, regardless of method of expression.

Daily caloric intake was determined in 16 subjects in the PS-QUAD group and in 8 subjects in the NPS-QUAD group. On average, the PS and nonPS groups with quadriplegia were not significantly different for caloric intakes (1744 ± 161.07 vs. $1546 \pm 157.90 \text{ kcal/day}$, respectively), or for recommendations (1842 ± 148.33 vs. $1716 \pm 259.00 \text{ kcal/day}$, respectively; 23 kcal/kg/day , Endersbe et al., 1989).

Conclusions: PSs increase the relative energy requirement in individuals with quadriplegia. Quantification of energy expenditures and providing these energy needs is vital for optimal care in individuals with quadriplegia and pressure sores.

Sp7. Liver Enzymes and Viral Hepatitis B in Veterans with Spinal Cord Injury. A. Rozman, A. Spungen, A. Rosman, H. Drexler, W. Bauman. The Spinal Cord Damage Research Center and Departments of Medicine and Rehabilitation Medicine, Mount Sinai Medical Center, New York, NY, Spinal Cord Injury and Medical Services, Veterans Affairs Medical Center, Bronx, NY.

Statement of the Problem: Patients with spinal cord injury (SCI) have an increased incidence of various health problems, including infections. This study determined the prevalence of abnormal liver function tests (LFTs) and viral hepatitis B (HBV) seropositivity in an urban veteran population with SCI.

Methods: Eighty patients with SCI (44 chronic inpatients and 36 outpatients) had the following tests performed: LFTs and HBsAg, anti-HBsAb, anti-HBcAb, HBeAg, and anti-HBeAb. Seventy-seven nonalcoholic, able-bodied medical clinic patients, prescreened to exclude the standard risk factors for HBV infection, were studied for seropositivity as controls.

Results: Abnormal LFTs [as defined by an elevation in one or more of the following: aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT) and alkaline phosphatase (Alk Phos)] was found in 64% of the inpatients compared with 39% of the outpatients with SCI and 32% of ambulatory controls ($p < 0.005$). In addition, the mean $\pm$ SEM levels of Alk Phos and GGT were significantly higher in SCI in patients compared to SCI outpatients and non-SCI controls (133 ± 9.8 vs. 85 ± 3.9 , 101 ± 6.9 , $p < 0.0005$ and 96 ± 20.1 vs. 34 ± 5.4 , 47 ± 8.3 , $p < 0.005$, respectively). Seropositivity for HBV was found in 39% of the chronic inpatients, 17% of the outpatients with SCI, and 22% of the controls. A significant difference was noted for HBV infection between the inpatient and outpatient groups with SCI ($p < 0.05$) and between SCI inpatients and ambulatory controls ($p = 0.05$); no significant difference was found between SCI outpatients and controls. Abnormal LFTs was not a predictor of HBV seropositivity in any of the groups. However, the GGT level was significantly greater in the HBV seropositive ($n = 40$) population than in the hepatitis B seronegative ($n = 117$) population (85

± 19 vs. 48 ± 7 , $p < 0.05$, respectively). This trend also existed for the SCI population, in which the GGT level was significantly greater in HBV seropositive ($n = 23$) patients than in the seronegative ($n = 57$) patients (107 ± 31 vs. 52 ± 11 , $p < 0.05$, respectively). Of the subgroup of SCI inpatients with seropositivity for HBV, there were 65% with paraplegia compared with 35% with quadriplegia ($p = 0.07$).

Conclusions: This study suggests that the profile for an individual who is at increased risk for HBV infection is a patient with SCI who is a chronically hospitalized patient with an elevated GGT level.

Sp8. Metabolic Responses to Maximal Arm Ergometry in Paraplegia and Able-Bodied Controls. A. Spungen, Y. Zhong, W. Bauman. Spinal Cord Damage Research Center, Departments of Medicine and Rehabilitation Medicine, Mount Sinai Medical Center, New York, NY, and Veterans Affairs Medical Center, Bronx, NY.

Statement of the Problem: The purpose of this study was to investigate the physiologic response to submaximal and maximal arm ergometry exercise and recovery in subjects with paraplegia compared with able-bodied controls.

Methods: Fourteen male subjects with paraplegia (PARA) and nine nonparalyzed male subjects (controls) were maximally exercised using an incremental arm ergometry stress test. Baseline values for gas exchange, heart rate (HR), and venous plasma lactate (LA) were obtained. During each minute of exercise, gas exchange, heart rate, work (watts), and LA (mmol/L) were measured. The incremental exercise test consisted of 1-minute stages with a cranking frequency of 60 rpm, beginning at 12 watts and increasing by 12 watts per minute until test termination. Oxygen consumption (VO_2) and carbon dioxide production (VCO_2) were calculated from mixed expired O_2 and CO_2 concentrations. Subjects exercised until they were unable to maintain the workload (i.e., 60 rpm at the current work rate). Only those studies were considered to be a maximal exercise test in which the subject reached $\geq 85\%$ of maximum predicted heart rate ($220 - \text{age}$) and achieved a respiratory exchange ratio of ≥ 1.10 . During recovery, LA was measured at 1, 2, 3, 5, 10, 15, 20, and 30 minutes.

Results: Results are reported as mean $\pm$ SEM. Age, height, weight, and body surface area were not significantly different for the PARA vs. control groups. The average peak (PK) exercise values were lower in the PARA group than the control group for workload (96 ± 6 vs. 136 ± 9 watts, $p < 0.003$), VO_2 (1575 ± 108 vs. 2201 ± 140 ml/min, $p < 0.002$), $\text{VO}_2\%$ of predicted (55 ± 3 vs. $73 \pm 4\%$, $p < 0.002$), VE (68.5 ± 5.2 vs. 91.7 ± 7.6 L/min), O_2 pulse (O_2p) (9.6 ± 0.5 vs. 12.9 ± 0.8 ml/beat, $p < 0.002$) and LA (12.4 ± 1.0 vs. 16.4 ± 1.2 mmol/L, $p < 0.02$), respectively. However, by using multiple regression to control for differences in PK watts, none of the PK values for HR, VO_2 , RER, VE, O_2p or LA remained significantly different between the PARA and control groups. There were no significant differences found between the groups for PK HR, PK HR% of predicted, and PK respiratory exchange ratio (RER). LA was significantly lower ($p < 0.05$) during each minute of recovery in the PARA group than in the control group, but once corrected for PK watts, these differences were no longer significant. Comparing the values of HR, VO_2 , RER, VE, O_2p and LA at each incremental level of submaximal work between the groups revealed only HR

to be different, the PARA group being significantly higher ($p < 0.05$) than the control group.

Conclusions: Controlling for peak workload, the physiological response to maximal arm ergometry exercise stress testing and recovery is not significantly different between healthy subjects with paraplegia and healthy controls. Heart rate was significantly higher in subjects with paraplegia compared with the controls at submaximal workloads, possibly due to reduced cardiopulmonary fitness and/or increased venous pooling in the lower extremities.

Sp9. Serum IGF-I Levels in Subjects with Spinal Cord Injury Are Higher in Growth Hormone GHRH Responders than Nonresponders. Y. Zhong, H. Drexler, A. Spungen, P. Tsitouras, and W. Bauman. Spinal Cord Damage Research Center, Department of Medicine, Mount Sinai School of Medicine, New York, NY, Veterans Affairs Medical Center, Bronx, NY.

Statement of the Problem: A blunted growth hormone response to IV arginine (ARG) was shown (Bauman et al., *Horm Metab Res*, 1994) in subjects with chronic spinal cord injury (SCI). Various pathologic conditions exhibit diminished or absent growth hormone (GH) release to some GH stimuli but not to others. GH release has been shown to decline with advancing age. Persons with SCI have been postulated to represent a model of premature aging.

Methods: We investigated the GH response on separate days to IV ARG and growth hormone releasing hormone (GHRH) in 8 SCI subjects. The peak GH (pGH) response to both secretagogues was compared. The relationships between the pGH response and advancing age or duration of injury (DOI) were studied.

Results: Values are expressed as mean $\pm$ SEM. The age of the group was 38.4 ± 3.3 y; DOI, 15.0 ± 3.3 y; BMI, 26.5 ± 2.1 kg/m². At 08:00 hours, ARG (30 g per subject) was infused IV over 30 minutes. On a separate morning, GHRH (1 $\mu\text{g/kg}$) was administered IV. For each provocative test, blood was drawn at -30, 0, 30, 60, 90, and 120 minutes. Serum GH was measured by RIA (ICN Biomedicals, Inc, Costa Mesa, CA). Data were analyzed by paired t-test for the comparison between stimulation tests. Simple and multiple regression models were used to determine effects of age and DOI on pGH.

Results: After ARG stimulation, 3 of 8 subjects were GH responders (ARG_{RESP}), whereas to GHRH, 5 of 8 subjects were $\text{GHRH}_{\text{RESP}}$. All ARG_{RESP} plus 2 $\text{ARG}_{\text{NONRESP}}$ were $\text{GHRH}_{\text{RESP}}$. No significant differences were found between ARG_{RESP} and $\text{ARG}_{\text{NONRESP}}$ for age or DOI. However, $\text{GHRH}_{\text{RESP}}$ had a shorter DOI than the $\text{GHRH}_{\text{NONRESP}}$ (9.8 ± 2.9 vs. 23.7 ± 3.4 y, $p < 0.05$). Of note, $\text{GHRH}_{\text{RESP}}$ had higher serum IGF-I levels than $\text{GHRH}_{\text{NONRESP}}$ (293 ± 33 vs. 132 ± 34 ng/ml, $p < 0.05$), whereas a significant difference was not found between ARG_{RESP} and $\text{ARG}_{\text{NONRESP}}$. In a multiple regression model for DOI on GHRH pGH, controlling for age, the partial r for DOI was 0.69, the multiple R being 0.80 ($p = 0.07$). Thus, age was removed from the model. Simple regression of DOI on GHRH pGH response was significant ($r = 0.79$, $p = 0.02$).

Conclusions: Neither age nor DOI were predictive of pGH response to ARG. Thus, (1) $\text{GHRH}_{\text{RESP}}$ had higher serum IGF-I levels than $\text{GHRH}_{\text{NONRESP}}$, and (2) DOI was predictive of pGH response to GHRH. These findings are compatible with SCI being a model of premature aging.

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The Department of Rehabilitation Medicine
The Mount Sinai School of Medicine (CUNY)

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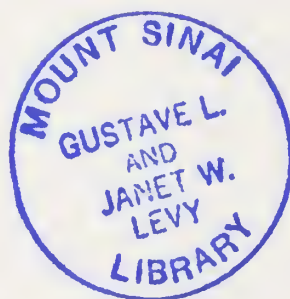
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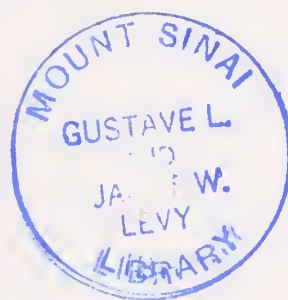
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